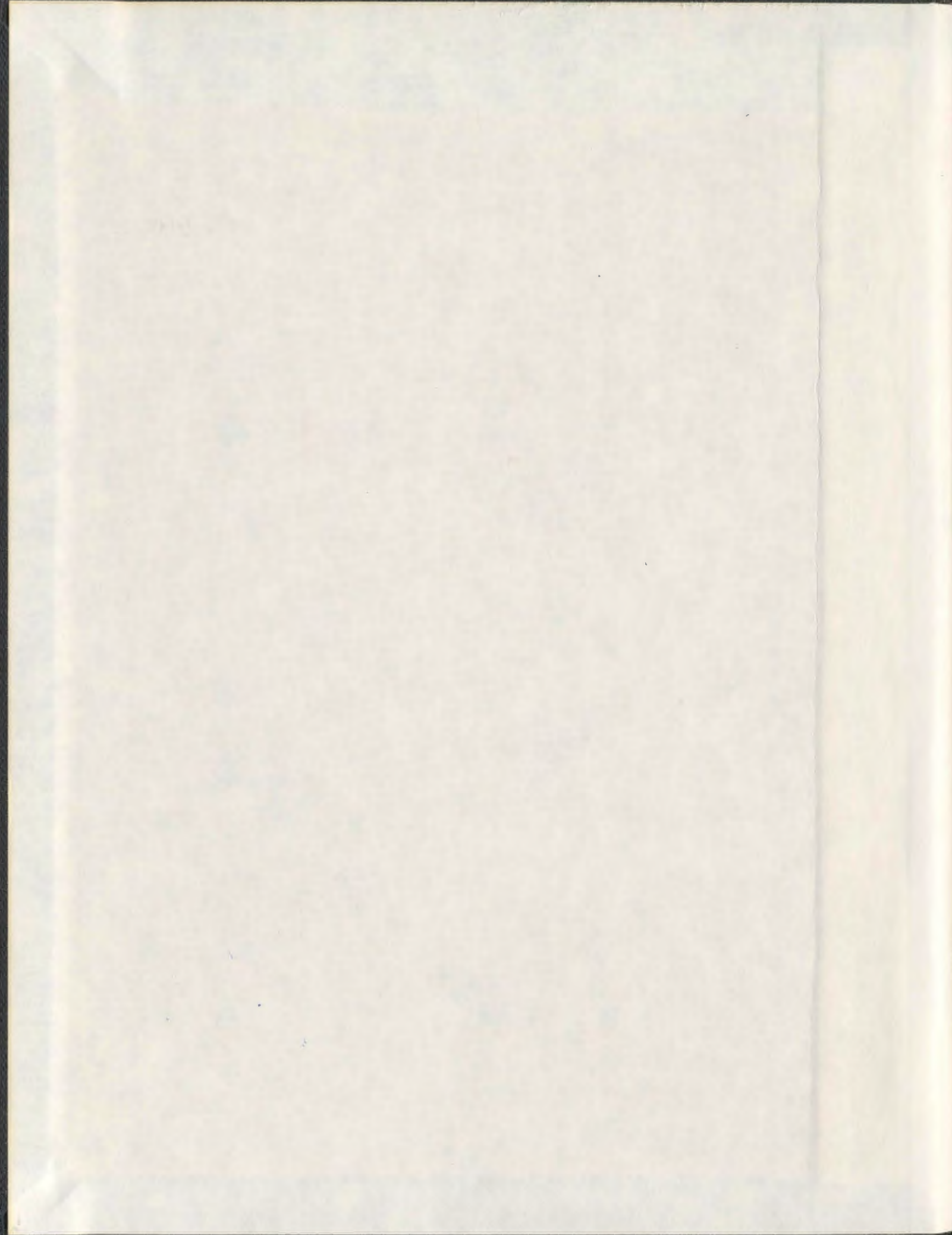# INVERSE ELECTRON DEMAND DIELS–ALDER REACTIONS OF COUMARIN-FUSED ELECTRON DEFICIENT DIENES

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INVERSE ELECTRON DEMAND DIELS-ALDER REACTIONS OF COUMARIN-FUSED ELECTRON DEFICIENT DIENES

by

© Amit A. Kudale

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To my parents

Abstract

The Diels-Alder reaction is one of most powerful reactions for the construction of six-membered rings. As compared with the normal Diels-Alder reaction ($HOMO_{diene}$-$LUMO_{dienophile}$), the inverse electron demand Diels-Alder (IEDDA) reaction ($HOMO_{dienophile}$-$LUMO_{diene}$) has been explored to a far lesser extent. The synthesis of electron deficient dienes for IEDDA reactions is one of the major challenges in the development of IEDDA reactions. This thesis deals mainly with the exploration and applications of electron deficient coumarin-fused dienes in the IEDDA reactions.

For the study of electron deficient coumarin-fused 2-azadienes, various 3-aminocoumarins were desired. In Chapter 1, a convenient synthesis of 3-aminocoumarins is described. A few azadienes were synthesized by the condensation of some of the 3-aminocoumarins and salicylaldehyde derivatives. These dienes were used in a study of proton-coupled electron transfer process in collaboration with Dr. D. W. Thompson.

A multicomponent synthesis of 1,2,3,4-tetrahydropyrido[2,3-c]coumarins, which involves an IEDDA reaction, was developed. Various *in situ*-generated coumarin-fused 2-azadienes react with electron rich dienophiles in the presence of Yb(OTf)$_3$ to afford, after IEDDA reaction and tautomerization of the initial adduct, 1,2,3,4-tetrahydropyrido[2,3-c]coumarins. Some aspects of the chemistry of these products were investigated. This discussion is covered in Chapter 2.

Chapter 3 includes details of an exploratory study of intramolecular IEDDA reaction of the coumarin-fused 2-azadienes and its application to diversity-oriented synthesis of complex pentacyclic heterocycles. This reaction generally proceeds with very high diastereoselectivity in favor of the diastereomer arising from an *exo* transition state.

Efforts toward the synthesis of a structurally interesting naphtho-fused [7]helicene are discussed in Chapter 4. A synthetic route to some key intermediates for this target has been established.

In Chapter 5, an iterative strategy for the synthesis of a coum[5]isophenacene, a novel structural motif, is described. Some groundwork for future studies has been accomplished during these efforts.

Acknowledgements

I am thankful to my Ph.D. supervisor, Prof. Graham J. Bodwell, who not only made chemistry enjoyable but also brought me up to a level that I am writing this thesis. His guidance, encouragement and patience throughout my academic program have been a great driving force. His passion, dedication and determination towards research will always inspire me to do better. I feel honored to have worked under the guidance of Prof. Bodwell during the most important phase of my career.

I was fortunate to have an opportunity to work with Dr. Ivo Starý and Dr. Irena Stará at the Academy of Sciences of the Czech Republic in Prague, Czech Republic. The support and friendly environment in their laboratory was overwhelming. I also owe many thanks to the members of my supervisory committee, Dr. John Bridson, Dr. Karen Hattenhauer and Dr. Yuming Zhao for valuable suggestions during the research work and writing of this thesis.

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Technical support provided by the members of C-CART was crucial for making progress in the research. I would like to specially thank Ms. Linda Winsor for prompt work on HRMS spectra for most of the compounds reported in this thesis. I am very

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Last, I would like to thank the most important people in my life, my parents Mr. Ashok and Mrs. Shila Kudale and my brothers Mr. Atish and Mr. Ajay Kudale for the infinite love they have given me. This accomplishment would not have been possible without their sacrifice and support over the years. I am truly indebted to them and I owe everything in my life to them.

Amit A. Kudale

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

Abs	Absolute
APCI	Atmospheric pressure chemical ionization
calcd	Calculated
CAN	Ceric (IV) ammonium nitrate
COSY	Correlation spectroscopy
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DHF	2,3-Dihydrofuran
DHP	3,4-Dihydro-2*H*-pyran
DMAP	4-(Dimethylamino)pyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DoM	Directed *ortho* metallation
dr	Diastereomeric ratio
eq	Equation
equiv	Equivalents
ESI	Electrospray ionization
EWG	Electron withdrawing group
GC/MS	Gas chromatography/mass spectrometry

HMBC	Heteronuclear multiple bond coherence
HMQC	Heteronuclear multiple quantum coherence
HSQC	Heteronuclear single quantum coherence
HRMS	High resolution mass spectrometry
IEDDA	Inverse electron demand Diels-Alder
IMDA	Intramolecular Diels-Alder
IR	Infra red
IUPAC	International Union of Pure And Applied Chemistry
LC/MS	Liquid chromatography/mass Spectrometry
Lit	Literature
MCR	Multicomponent reaction
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PCET	Proton-coupled electron transfer
ppm	Parts per million
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
tlc	Thin layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Tetramethylsilane
TMSCl	Chlorotrimethylsilane
UV	Ultra violet

Chapter 1. Hydrolysis-free Synthesis of 3-Aminocoumarins and Synthesis of Coumarin-fused 2-Azadienes

1.1 Introduction

The coumarin system is present in a very broad range of natural and non-natural products of biological interest.[1] The 3-aminocoumarin motif, while considerably less prevalent, can nonetheless be found in a number of naturally occurring antibiotics, such
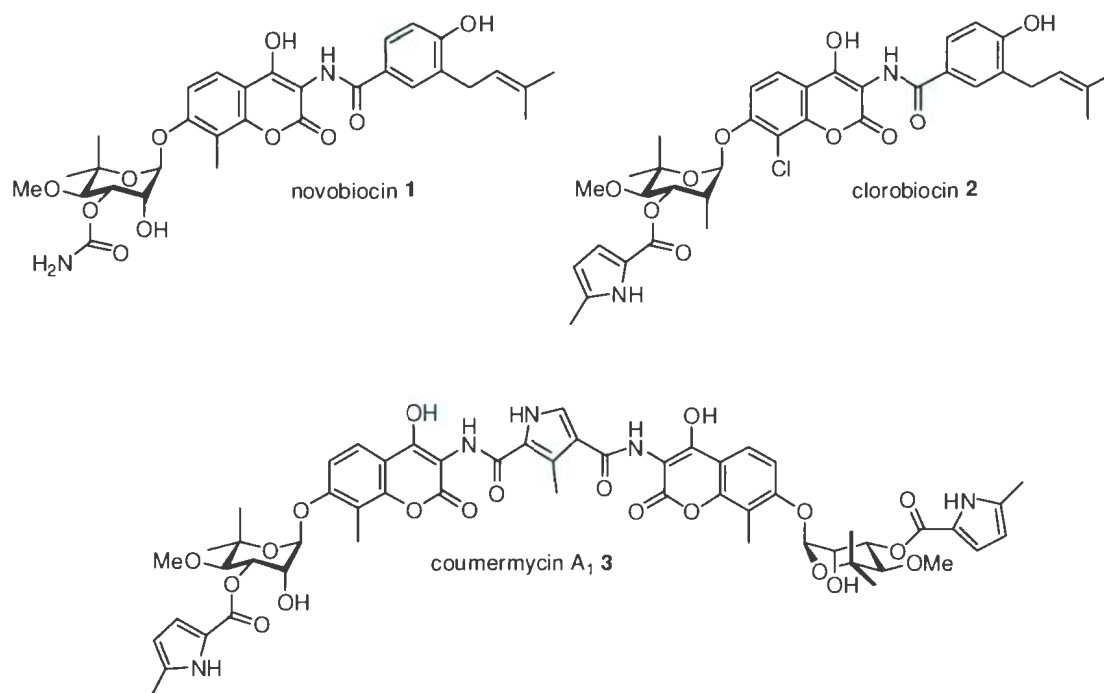
FIGURE 1.1 Natural Antibiotics Containing 3-Aminocoumarin

as novobiocin (**1**),[2] clorobiocin (**2**)[3] and coumermycin A_1 (**3**)[4] (Fig. 1.1).

Derivatives of 3-aminocoumarins have been found to possess biological activity, including CNS depressant,[5] antibacterial,[6] antiallergic[7] and insect-growth-regulatory.[8] Moreover, 3-aminocoumarin and its derivatives are also known to exhibit interesting photochemical behavior and have found application as fluorescent markers.[9]

Although various methods have been reported for the synthesis of 3-aminocoumarins or related compounds,[10] reproducibility has sometimes been a problem, as experienced by us and others.[11] The final step of these syntheses is typically the hydrolysis of a 3-acetamidocoumarin, which can result in the formation of a 3-hydroxycoumarin, both under acidic and basic conditions.[12]

1.2 Results and Discussion

1.2.1 Synthesis of the Parent 3-Aminocoumarin

For the parent 3-aminocoumarin (**7a**), the synthesis commenced with the conversion of commercially available (or easily prepared from salicylaldehyde and *N*-acetylglycine[13]) 3-acetamidcoumarin (**5a**) to Boc-protected 3-aminocoumarin (**6a**) using the method of Burk and Allen[14] in 94% yield. This one-pot procedure, which was originally developed for amino acids, involves an acylation-deacylation sequence in which an *N*-acetyl compound is reacted with di-*t*-butyl dicarbonate in the presence of DMAP to give an imide, followed by reaction with hydrazine hydrate to remove the acetyl group. The resulting *t*-butyl carbamate (**6a**) could then be easily converted to 3-aminocoumarin (**7a**) in high yield (99%) under anhydrous conditions through the action

of 15% TFA/CHCl$_3$ (Scheme 1.1). In our hands, this method has proved to be very reproducible and we have prepared up to 15 g of 3-aminocoumarin in a single run.

SCHEME 1.1 General Synthesis of 3-Aminocoumarins
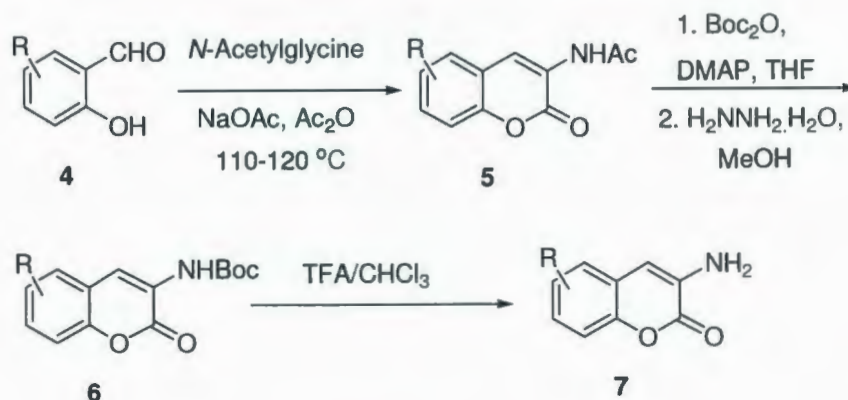
1.2.2 Optimization for the Condensation of Salicylaldehyde with *N*-Acetylglycine

For the synthesis of substituted 3-aminocoumarins, suitably substituted 3-acetamidocoumarins (**5**) were required. Being commercially unavailable, it was envisaged that these compounds could be prepared from the corresponding salicylaldehyde and *N*-acetylglycine.[13] Since the yield for parent 3-acetamidocoumarin (**5a**) is low (27%) using this method, efforts were made to optimize the reaction conditions for the conversion of salicylaldehyde (**4a**) into **5a**. After varying reaction time, temperature, number of equivalents of *N*-acetylglycine and sodium acetate, it was found that the use of 4.0 equivalents of sodium acetate and 1.0 equivalent of *N*-acetylglycine at 110-120 °C for 3.5 hours gave the best yield (46%) for the parent 3-acetamidocoumarin (**5a**) (Entry 6, Table 1.1).

TABLE 1.1 Optimization for the Synthesis of 3-Acetamidocoumarin
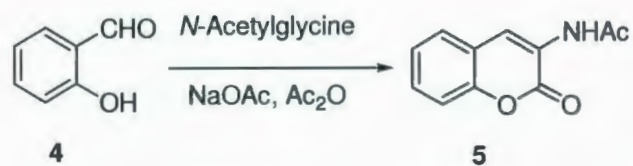
Entry	Ratio of reactants 4 : *N*-acetylglycine : NaOAc	Temperature (°C)	Time (h)	Yield[a] (%)
1	1.0 : 1.0 : 1.0	110-120	3.5 h	29
2	1.0 : 1.5 : 1.0	110-120	3.5 h	35
3	1.0 : 3.0 : 1.0	110-120	3.5 h	30
4	1.0 : 1.0 : 2.0	110-120	3.5 h	35
5	1.0 : 1.0 : 3.0	110-120	3.5 h	38
6	1.0 : 1.0 : 4.0	110-120	3.5 h	46
7	1.0 : 1.0 : 5.0	110-120	3.5 h	42
8	1.0 : 1.0 : 7.5	110-120	3.5 h	39
9	1.0 : 2.0 : 4.0	110-120	3.5 h	42
10	1.0 : 1.0 : 4.0	70-80	3.5 h	39
11	1.0 : 1.0 : 4.0	110-120	7 h	44
12	1.0 : 1.0 : 4.0	110-120	2 h	34

[a] Isolated yields

4

1.2.3 Synthesis of Various 3-Aminocoumarin Derivatives

Employing the optimized reaction conditions (Table 1.1, Entry 6) for a series of substituted salicylaldehydes (commercially available or easily prepared by known formylation protocols[15]) afforded the corresponding 3-acetamidocoumarins (**5b-i**) (Table 1.2). The yields for these reactions were variable. Poor yields were obtained when an electron-donating group was situated *para* to the aldehyde function of the starting salicylaldehyde (Table 1.2, Entries 6 and 8). Otherwise, the yields ranged from 40-69%. When the starting material was 4-hydroxysalicylaldehyde (Table 1.2, Entry 8), *O*-acylation also took place, giving 7-acetoxy-3-acetamidocoumarin (**5h**) as the product.

The next step involved conversion of the acetamide to a *t*-butyl carbamate. Burk and Allen's one-pot protocol was then employed to afford the Boc-protected 3-aminocoumarins (**6b-i**) (Table 1.3). Under these conditions, the acetoxy group in **5h** was converted back to a hydroxy group (Table 1.3, Entry 8). For the most part, the yields were high. As above, the yields of the products with donor groups at the 7-position (Table 1.3, Entries 6 and 8) were anomalously low.

TABLE 1.2 Condensation of Salicylaldehydes with *N*-Acetylglycine
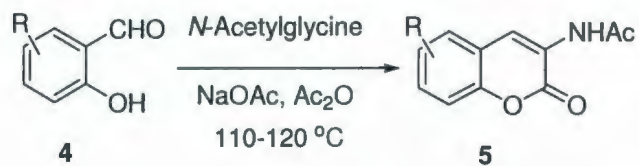
Entry	R	Product	Yield^a (%)
1	H	**5a**	46
2	6-Br	**5b**	69
3	6-Me	**5c**	42
4	6-NO$_2$	**5d**	69
5	6-OMe	**5e**	40
6	7-OMe	**5f**	20
7	8-OMe	**5g**	69
8	7-OAc	**5h**	21^b
9	5,6-benzo	**5i**	63

^{a} Isolated yields, ^{b} 4-HOC$_6$H$_4$CHO was the starting material in this reaction.   The OH group undergoes acetylation under the reaction conditions.

TABLE 1.3 Conversion of 3-Acetamidocoumarins (**5**) into Boc-protected 3-

Aminocoumarins (**6**)
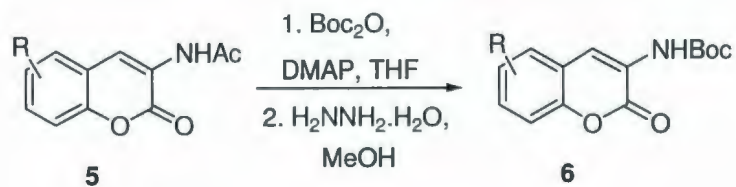
Entry	R	Product	Yield^a (%)
1	H	**6a**	94
2	6-Br	**6b**	87
3	6-Me	**6c**	90
4	6-NO$_2$	**6d**	93
5	6-OMe	**6e**	93
6	7-OMe	**6f**	58
7	8-OMe	**6g**	92
8	7-OH	**6h**	50
9	5,6-benzo	**6i**	95

^{a} Isolated yields

Removal of the Boc-group using 15% $TFA/CHCl_3$ then afforded the 3-aminocoumarins (**7b-i**) in generally very good yields (58-96%) (Table 1.4). In no case

TABLE 1.4 Removal of the Boc Group

Entry	R	Product	Yield^a (%)
1	H	**7a**	99
2	6-Br	**7b**	67
3	6-Me	**7c**	96
4	$6\text{-}NO_2$	**7d**	89
5	6-OMe	**7e**	95
6	7-OMe	**7f**	58^b
7	8-OMe	**7g**	80
8	7-OH	**7h**	96
9	5,6-benzo	**7i**	65

^{a} Isolated yields, ^{b} 37% **6f** recovered after 3 h.

8

was any 3-hydroxycoumarin detected. Clearly, the use of Boc as a protecting group is crucial because it can be removed under anhydrous conditions. The optimal reaction times for preparing the desired 3-aminocoumarins were found to be generally between 3 and 4.5 hours at room temperature. Longer reaction times resulted in a decrease in the yields of desired 3-aminocoumarins and the formation of the corresponding 3-trifluoroacetamidocoumarin (**8**) (Scheme 1.2).

For the parent system, 3-trifluoroacetamidocoumarin (**8a**) was isolated in 14% yield after a reaction time of 31 hours. Evidently, the 3-aminocoumarin, once formed, is acylated by the solvent. Indeed, stirring pure 3-aminocoumarin (**7a**) in 15% TFA/CHCl$_3$ at room temperature resulted in the slow formation of **8a** (tlc analysis). After stirring for 7 days, roughly equivalent amounts of **7a** and **8a** were present in solution (tlc analysis) and, after a further day's reaction at reflux, trifluoroacetamidcoumarin (**8a**) was isolated in 68% yield.

SCHEME 1.2 Formation of 3-Trifluoroacetamidocoumarin **8**

9
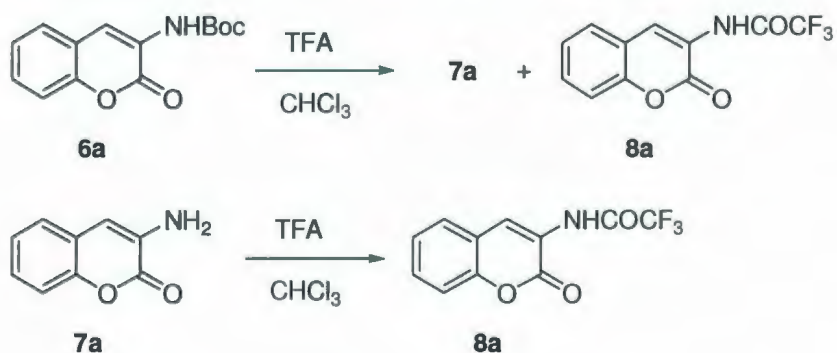
1.2.4 Synthesis of Coumarin-fused 2-Azadienes

In connection with our involvement in the study of inverse electron demand Diels-Alder (IEDDA) reactions, electron deficient dienes **9a** and **10a** were prepared previously (Scheme 1.3).[11a] Although these dienes did not participate in IEDDA reaction with electron rich dienophiles such as an enamine, they contained an interesting chromophore for proton-coupled electron transfer (PCET) process. In collaboration with Dr. David Thompson's research group, photophysical studies of **9a** and **10a** were performed. Based on the initial results, some derivatives of these dienes were desired that would help in understanding of the PCET process in these dienes.

SCHEME 1.3 Synthesis of **9a** and **10a**
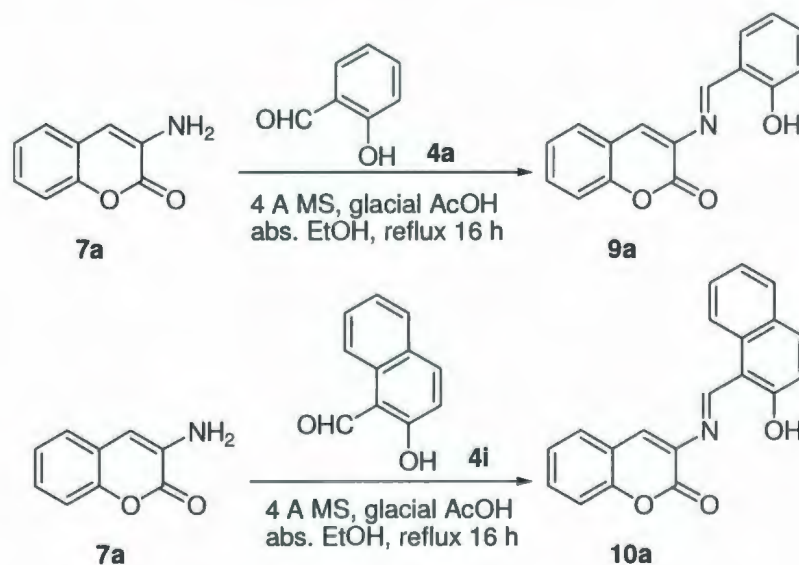
The following derivatives of the coumarin-fused 2-azadienes were prepared by reacting suitable 3-aminocoumarin derivative with salicylaldehyde (**4a**) (Table 1.5) or 2-hydroxynaphthaldehyde (**4i**) (Table 1.6) in acceptable yields. The details regarding the photophysical studies of these molecules are outside the scope of this thesis. These results will be published in collaboration with Dr. David Thompson's research group in the future.

TABLE 1.5 Synthesis of 2-Azadienes **9b-9d**
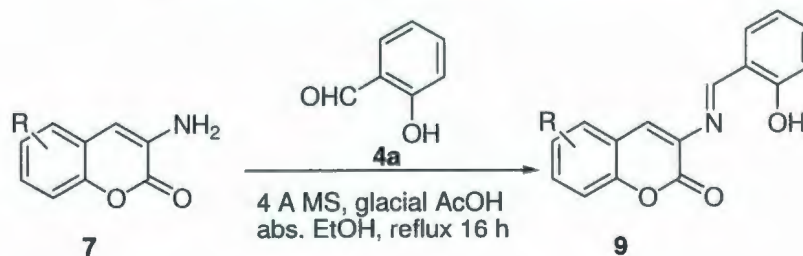
Entry	R	Product	Yield^a (%)
1	6-OMe	**9b**	72
2	6-NO$_2$	**9c**	71
3	5,6-Benzo	**9d**	57

^{a} Isolated yields

TABLE 1.6 Synthesis of 2-Azadienes **10a-10d**
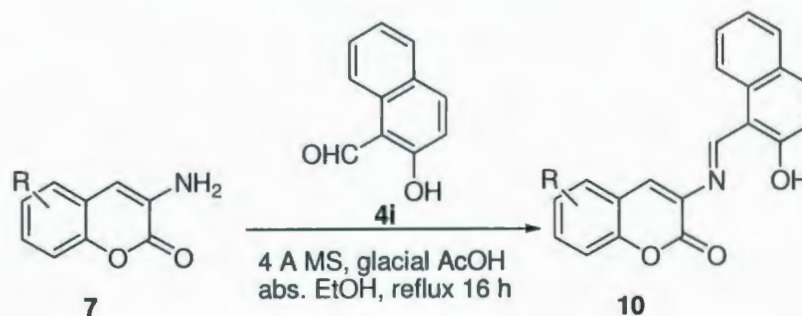
Entry	R	Product	Yield^a (%)
1	H	**10a**	42
2	6-OMe	**10b**	64
3	6-NO$_2$	**10c**	68
4	5,6-Benzo	**10d**	70

^{a} Isolated yields

1.3 Conclusion

In conclusion, a hydrolysis-free method for the synthesis of 3-aminocoumarins has been developed. It can be used to prepare multigram quantities of various 3-aminocoumarins and does not result in the formation of any 3-hydroxycoumarins. Coumarin-fused 2-azadienes have also been prepared for collaborative studies with Dr. David Thompson's research group.

1.4 Experimental

1.4.1 General Methods

All reactions were carried out in oven-dried glassware without inert gas protection. THF was dried and distilled over sodium/benzophenone. ACS grade chloroform was used for deprotection reactions. Distilled methanol was used in procedure B. All other chemicals, including solvents, were used as received, without further purification. Thin layer chromatography (tlc) was performed on MN PolyGram precoated silica gel plates using 254 nm UV visualization. Melting points were recorded on Fisher-Johns apparatus and are uncorrected. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and HRMS techniques. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE spectrometer at 500.133 MHz and 125.770 MHz, respectively. Peaks reported are relative to internal standards: TMS ($\delta = 0.00$) for ^{1}H and CDCl$_3$ ($\delta = 77.23$) or DMSO-d_6 ($\delta = 39.51$) for ^{13}C spectra. Reported multiplicities are apparent. Infrared spectra were obtained on Bruker Tensor 27 instrument using neat samples. Low-resolution mass spectra were obtained using using HP5970 GC/MSD or Agilent 1100 series LC/MS chromatographic system and high-resolution mass spectra were obtained using Waters GCT Permier Micromass mass spectrometer. All known compounds were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy and reported melting point(s).

1.4.2 Representative Procedures

1.4.2.1 Representative Procedure A: 3-Acetamido-2*H*-chromen-2-one (5a)

5a
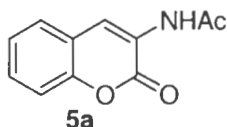
A mixture of salicylaldehyde **4a** (6.10 g, 50.0 mmol), *N*-acetylglycine (5.85 g, 50.0 mmol), anhydrous sodium acetate (16.40 g, 200.0 mmol) and acetic anhydride (25.0 mL) was heated at 110-120 °C for 3.5 h. The resulting brown solution was allowed to cool to room temperature and it solidified completely. Ice-cold water was added to the brown solid and the mass was broken up with a spatula. The resulting mixture was suction filtered and the solids were washed 2-3 times with cold water. The resulting solid was air dried, triturated with ethyl acetate, suction filtered and air dried again to afford 3-acetamidocoumarin **5a** as a pale yellow solid (4.21 g, 42%). The filtrate was then concentrated and purified by column chromatography on silica gel (30% ethyl acetate/hexanes) to afford 3-acetamidocoumarin **5a** (0.38 g, 4%). Combined Yield: 4.59 g, (46%). mp = 195-196 °C (ethanol) (Lit.[10c] 201.5 °C, Lit.[10a] 206 °C); δ_H(CDCl$_3$) = 8.68 (s, 1H), 8.06 (s, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.47-7.43 (m, 1H), 7.34-7.29 (m, 2H), 2.25 (s, 3H) ppm; δ_C(CDCl$_3$) = 169.6, 158.9, 150.1, 129.8, 128.0, 125.3, 124.2, 123.4, 120.0, 116.5, 24.9 ppm.

Note: For practical purposes, filtrates from different reactions can be combined and chromatographed together when a sufficient amount has been collected.

1.4.2.2 Representative Procedure B: (2-Oxo-2H-chromen-3-yl)carbamic acid *tert*-butyl ester (6a)

6a
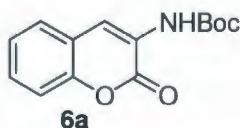
To a mixture of 3-acetamidocoumarin **5a** (5.00 g, 24.6 mmol) and DMAP (0.60 g, 4.9 mmol) in THF (125 mL), di-*tert*-butyl dicarbonate was added and the mixture was magnetically stirred at room temperature. The initial yellow suspension became a clear brown solution after 20 min. Hydrazine hydrate (3.83 mL, 123 mmol) was then added to the reaction mixture, followed by the addition of methanol (100 mL). The reaction mixture was stirred for a further 20 min, during which time it became orange. The solvents were removed under reduced pressure. The resulting sticky yellow mass was dissolved in dichloromethane and washed with 1 M aqueous HCl solution, 1 M aqueous CuSO$_4$ solution and saturated aqueous NaHCO$_3$ solution. Finally, the organic layer was washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure and chromatographed on silica gel (15% ethyl acetate/hexanes) to yield **6a** as a white solid (5.26 g, 94%). mp = 85-86 °C (chloroform/hexanes) (Lit.[10i] 85-86 °C); δ$_H$(CDCl$_3$) = 8.28 (s, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.41-7.39 (m, 2H), 7.32-7.28 (m, 2H),

1.54 (s, 9H) ppm; δ_C(CDCl$_3$) = 158.8, 152.7, 149.7, 129.2, 127.5, 125.3, 124.8, 120.6, 120.3, 116.5, 81.9, 28.4 ppm.

1.4.2.3 Representative Procedure C: 3-Amino-2*H*-chromen-2-one (7a)

7a
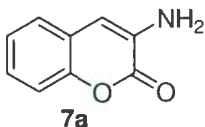
A solution of **6a** (25.0 g, 96.0 mmol) in 15% TFA/chloroform (1.17 L) was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel (30% ethyl acetate/hexanes) to yield 3-aminocoumarin **7a** as an off-white solid (15.25 g, 99%). mp = 135-136 ℃ (chloroform/hexanes) (Lit.[10a] 132-135 ℃); δ_H(CDCl$_3$) = 7.31-7.26 (m, 3H), 7.24-7.19 (m, 1H), 6.71 (s, 1H), 4.15 (s, 2H) ppm; δ_C(CDCl$_3$) = 159.6, 149.2, 132.2, 126.8, 125.3, 124.8, 121.4, 116.3, 111.1 ppm.

1.4.2.4 Representative Procedure D: 3-((2-Hydroxynaphthalen-1-yl)methyleneamino)-2*H*-chromen-2-one (10a)

10a
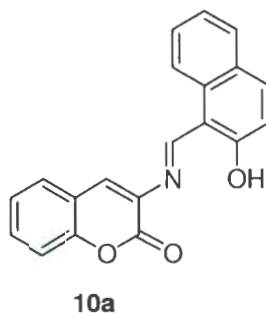
A mixture of **7a** (1.61 g, 10.0 mmol), **4i** (1.81 g, 10.5 mmol), 4 Å molecular sieves (~ 10 g) and glacial acetic acid (4 drops) in absolute ethanol (100 mL) was heated at reflux for 18 h. The reaction mixture turned from clear orange solution to a red suspension over the course of the reaction. It was allowed to cool to room temperature and the precipitate (along with molecular sieves) was filtered under suction to afford a red residue. It was washed with cold absolute ethanol. The red residue was separated from the molecular sieves by dissolving in dichloromethane. The solvent was removed under reduced pressure and the product was recrystallized from chloroform to afford **10a** as a red solid (1.32 g, 42%). mp = 227-228 °C (CHCl$_3$) (Lit.[11a] 224-226 °C); δ_H(CDCl$_3$) = 10.23 (s, 1H), 8.20 (d, J = 9.1 Hz, 1H), 7.86 (d, J = 9.1 Hz, 1H), 7.76-7.73 (m, 2H), 7.59-7.53 (m, 3H), 7.42-7.33 (m, 3H), 7.14 (d, J = 9.3 Hz, 1H) ppm; δ_C(CDCl$_3$) = 168.0, 159.6, 158.1, 152.1, 137.1, 133.4, 131.4, 131.3, 130.9, 129.5, 128.6, 128.0, 127.9, 125.2, 124.2, 121.2, 119.9, 119.8, 119.7, 116.7, 110.0 ppm.

17

1.4.3 Synthesis and Characterization for Individual Compounds

3-Acetamido-6-bromo-2*H*-chromen-2-one (5b)

5b
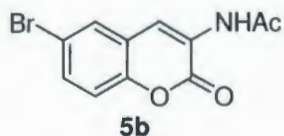
According to representative procedure A, 5-bromosalicylaldehyde (5.03 g, 25.0 mmol), *N*-acetylglycine (2.92 g, 25.0 mmol), anhydrous sodium acetate (8.20 g, 100 mmol) and acetic anhydride (12.8 mL) afforded **5b** as an off-white solid (4.84 g, 69%). mp = 262-263 °C (ethyl acetate/hexanes) (Lit.[11b] 261-262 °C); δ_H(CDCl$_3$) = 8.60 (s, 1H), 8.07 (s, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.53 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.21 (d, *J* = 9.0 Hz, 1H), 2.25 (s, 3H) ppm; δ_C(CDCl$_3$) = 169.6, 158.4, 148.9, 132.6, 130.2, 125.0, 121.8 (2C), 118.3, 118.2, 25.0 ppm.

3-Acetamido-6-methyl-2*H*-chromen-2-one (5c)

5c
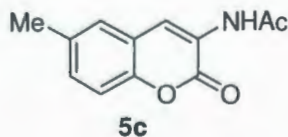
According to representative procedure A, 5-methylsalicylaldehyde (5.00 g, 36.7 mmol), *N*-acetylglycine (4.30 g, 36.7 mmol), anhydrous sodium acetate (12.05 g, 146.8 mmol) and acetic anhydride (25.0 mL) afforded **5c** as a white solid (3.38 g, 42%). mp = 209-212 °C (ethyl acetate/hexanes) (Lit.[10d] 214 °C); δ_H(CDCl$_3$) = 8.62 (s, 1H), 8.05 (s, 1H), 7.30 (s, 1H), 7.24-7.21 (m, 2H), 2.41 (s, 3H), 2.24 (s, 3H) ppm; δ_C(CDCl$_3$) = 169.7, 159.3, 148.5, 135.3, 131.1, 128.0, 124.3, 123.7, 120.0, 116.5, 25.1, 21.3 ppm.

3-Acetamido-6-nitro-2*H*-chromen-2-one (5d)

5d
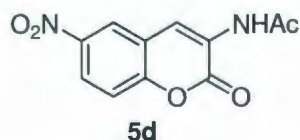
According to representative procedure A, 5-nitrosalicylaldehyde (1.85 g, 11.0 mmol), *N*-acetylglycine (1.30 g, 11.0 mmol), anhydrous sodium acetate (3.63 g, 44.0 mmol) and acetic anhydride (5.20 mL) afforded **5d** as a light brown solid (1.90 g, 69%). mp = 274-277 °C (ethyl acetate/hexanes) (Lit.[11b] 278 °C); δ_H(CDCl$_3$) = 8.76 (s, 1H), 8.44 (d, J = 2.4 Hz, 1H), 8.30 (dd, J = 9.2, 2.9 Hz, 1H), 8.10 (s, 1H), 7.46 (d, J = 9.1 Hz, 1H), 2.28 (s, 3H) ppm; δ_C(CDCl$_3$) = 169.7, 157.8, 153.2, 145.1, 125.8, 124.5, 123.6, 121.5, 120.6, 117.7, 25.0 ppm.

3-Acetamido-6-methoxy-2*H*-chromen-2-one (5e)

5e
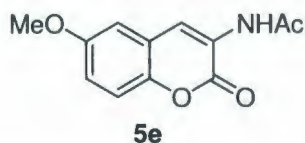
According to representative procedure A, 5-methoxysalicylaldehyde (7.60 g, 50.0 mmol), *N*-acetylglycine (5.85 g, 50.0 mmol), anhydrous sodium acetate (16.4 g, 200 mmol) and acetic anhydride (25.0 mL) afforded **5e** as an off-white solid (5.88 g, 40%). mp = 218-220 °C (ethyl acetate/hexanes) (Lit.[16] 212-214 °C); δ_H(CDCl$_3$) = 8.63 (s, 1H), 8.09 (s, 1H), 7.25 (d, J = 9.6 Hz, 1H), 7.01 (dd, J = 9.2, 2.6 Hz, 1H), 6.95 (d, J = 3.0 Hz, 1H), 3.85 (s, 3H), 2.25 (s, 3H) ppm; δ_C(CDCl$_3$) = 169.6, 159.0, 156.9, 144.5, 124.5, 123.3, 120.5, 117.7, 117.5, 109.9, 56.0, 24.9 ppm.

3-Acetamido-7-methoxy-2*H*-chromen-2-one (5f)

5f
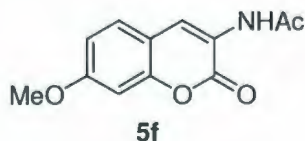
According to representative procedure A, 4-methoxysalicylaldehyde (2.00 g, 13.1 mmol), *N*-acetylglycine (1.54 g, 13.1 mmol), anhydrous sodium acetate (4.31 g, 52.5 mmol) and acetic anhydride (6.20 mL) afforded **5f** as a pale yellow solid (0.61 g, 20%) .

mp = 234-235 °C (ethyl acetate/hexanes) (Lit.[10d] 230 °C, Lit.[16] 235-237 °C); δ_H(CDCl$_3$) = 8.64 (s, 1H), 7.95 (s, 1H), 7.41 (d, J = 7.8 Hz, 1H), 6.89 (dd, J = 8.3, 2.5 Hz, 1H), 6.83 (d, J = 2.9 Hz, 1H), 3.87 (s, 3H), 2.23 (s, 3H) ppm; δ_C(CDCl$_3$) = 169.4, 161.5, 159.3, 151.6, 128.9, 124.3, 121.8, 113.4, 113.3, 101.0, 56.0, 24.9 ppm.

3-Acetamido-8-methoxy-2*H*-chromen-2-one (5g)

5g
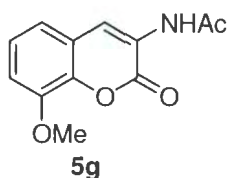
According to representative procedure A, 3-methoxysalicylaldehyde (7.60 g, 50.0 mmol), *N*-acetylglycine (5.85 g, 50.0 mmol), anhydrous sodium acetate (16.4 g, 200 mmol) and acetic anhydride (25.0 mL) afforded **5g** as an off-white solid (8.09 g, 69%). mp = 237-238 °C (ethyl acetate/hexanes) (Lit.[16] 237-239 °C); δ_H(CDCl$_3$) = 8.65 (s, 1H), 8.09 (s, 1H), 7.25-7.21 (m, 1H), 7.09 (d, J = 7.7 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 3.97 (s, 3H), 2.24 (s, 3H) ppm; δ_C(CDCl$_3$) = 169.6, 158.6, 147.2, 139.6, 125.3, 124.4, 123.6, 120.8, 119.6, 112.0, 56.4, 24.9 ppm.

3-Acetamido-7-acetoxy-2*H*-chromen-2-one (5h)

5h
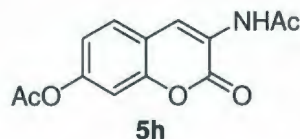
According to representative procedure A, 4-hydroxysalicylaldehyde (6.91 g, 50.0 mmol), *N*-acetylglycine (5.85 g, 50.0 mmol), anhydrous sodium acetate (16.40 g, 200.0 mmol) and acetic anhydride (25.0 mL) afforded **5h** as a light brown solid (2.73 g, 21%) . mp = 234-236 °C (ethyl acetate/hexanes) (Lit.[16] 231 °C); δ_H(CDCl$_3$) = 8.67 (s, 1H), 8.02 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.13 (s, 1H), 7.07 (dd, *J* = 8.8, 2.0 Hz, 1H), 2.34 (s, 3H), 2.24 (s, 3H) ppm; δ_C(CDCl$_3$) = 169.6, 169.1, 158.7, 151.6, 150.4, 128.6, 123.8, 123.0, 119.3, 117.9, 110.3, 24.9, 21.3 ppm; IR ν = 3341 (s), 1759 (s), 1720 (s), 1681 (s), 1611 (m), 1536 (m), 1431 (b), 1354 (m), 1284 (s), 1251 (s), 1206 (s), 1156 (s), 1118 (s), 1023 (m) cm^{-1}; MS *m/z* (relative intensity) = 261 (9, M$^+$), 219 (31), 177 (100), 149 (21), 65 (6) . HRMS [M$^+$] calcd for C$_{13}$H$_{11}$NO$_5$ 261.0637, found 261.0617.

3-Acetamido-5,6-benzo-2*H*-chromen-2-one (5i)

5i
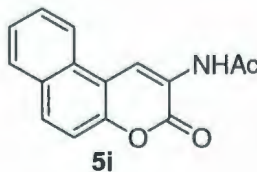
According to representative procedure A, 2-hydroxy-1-naphthaldehyde (1.72 g, 10.0 mmol), *N*-acetylglycine (1.17 g, 10.0 mmol), anhydrous sodium acetate (3.28 g, 40.0 mmol) and acetic anhydride (4.70 mL) afforded **5i** as an off-white solid (1.60 g, 63%) . mp = 247-250 °C (dichloromethane/hexanes) (Lit.[10d] 247 °C); δ_H(CDCl$_3$) = 9.53 (s, 1H), 8.33 (d, *J* = 7.7 Hz, 1H), 8.15 (s, 1H), 7.92-7.90 (m, 2H), 7.71-7.68 (m, 1H), 7.60-7.57 (m, 1H), 7.46 (d, *J* = 9.1 Hz, 1H), 2.30 (s, 3H) ppm; δ_C(CDCl$_3$) = 169.7, 159.0, 149.0, 131.1, 131.0, 129.4, 129.0, 128.1, 126.5, 124.3, 122.6, 119.7, 116.6, 114.5, 25.0 ppm.

(6-Bromo-2-oxo-2*H*-chromen-3-yl)carbamic acid *t*-butyl ester (6b)

6b
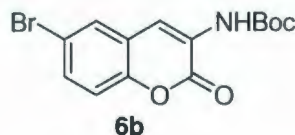
According to representative procedure B, **5b** (2.83 g, 10.0 mmol), DMAP (0.24 g, 2.0 mmol), di-*t*-butyl dicarbonate (9.12 g, 41.8 mmol) and hydrazine hydrate (2.43 mL, 50.0 mmol) afforded **6b** as a white solid (5.66 g, 87%). mp = 105-107 °C (ethyl acetate/hexanes) (Lit.[10i] 104-105 °C); δ_H(CDCl$_3$) = 8.19 (s, 1H), 7.58 (d, *J* = 1.7 Hz, 1H), 7.49 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.41 (s, 1H), 7.19 (d, *J* = 9.5 Hz, 1H), 1.53 (s, 9H) ppm; δ_C(CDCl$_3$) = 158.2, 152.5, 148.5, 131.9, 129.7, 125.7, 122.0, 118.9, 118.1, 118.0, 82.2, 28.4 ppm.

(6-Methyl-2-oxo-2*H*-chromen-3-yl)carbamic acid *t*-butyl ester (6c)

6c
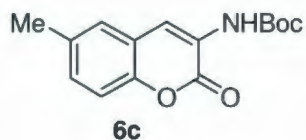
According to representative procedure B, **5c** (3.57 g, 16.5 mmol), DMAP (0.40 g, 3.3 mmol), di-*t*-butyl dicarbonate (15.02 g, 68.80 mmol) and hydrazine hydrate (4.00 mL, 82.3 mmol) afforded **6c** as a white solid (4.07 g, 90%) . mp = 133-134 °C; δ_H(CDCl$_3$) = 8.22 (s, 1H), 7.40 (s, 1H), 7.24 (m, 1H), 7.20 (m, 2H), 2.39 (s, 3H), 1.53 (s, 9H) ppm; δ_C(CDCl$_3$) = 159.0, 152.7, 147.9, 134.9, 130.2, 127.4, 124.7, 120.6, 120.0, 116.2, 81.8, 28.4, 21.1 ppm; IR ν = 3407(m), 1717(m), 1707(m), 1632(s), 1616(s), 1581(s), 1510(m), 1485(s), 1427(s), 1392(s), 1366(s), 1326(s), 1290(s), 1268(s), 1250(s), 1234(s), 1147(b), 1126(m), 1045(s), 1004(m) cm^{-1}; MS *m/z* (relative intensity) = 175 (100, M$^+$), 147 (57), 120 (28), 107 (7), 91 (8), 65 (18), 51 (15). HRMS [M$^+$] calcd for C$_{15}$H$_{17}$NO$_4$ 275.1158, found 275.1149.

(6-Nitro-2-oxo-2*H*-chromen-3-yl)carbamic acid *t*-butyl ester (6d)

6d

According to representative procedure B, **5d** (20.0 g, 92.5 mmol), DMAP (2.26 g, 18.5 mmol), di-*t*-butyl dicarbonate (84.39 g, 386.7 mmol) and hydrazine hydrate (22.5 mL, 463 mmol) afforded **6d** as a pale yellow solid (24.97 g, 93%) . mp = 117-118 °C (ethyl acetate/hexanes) (Lit.[10i] 132-134 °C); δ_H(CDCl$_3$) = 8.42 (d, J = 2.7 Hz, 1H), 8.39 (s, 1H), 8.29 (dd, J = 9.4, 2.9 Hz, 1H), 7.48-7.47 (m, 2H), 1.58 (s, 9H) ppm; δ_C(CDCl$_3$) = 157.5, 152.8, 152.3, 145.0, 126.5, 123.8, 123.0, 120.8, 118.6, 117.6, 82.7, 28.3 ppm.

(6-Methoxy-2-oxo-2*H*-chromen-3-yl)carbamic acid *t*-butyl ester (6e)

6e

According to representative procedure B, **5e** (2.79 g, 12.0 mmol), DMAP (0.29 g, 2.4 mmol), di-*t*-butyl dicarbonate (10.96 g, 50.16 mmol) and hydrazine hydrate (2.92 mL, 60.0 mmol) afforded **6e** as a white solid (3.26 g, 93%). mp = 164-165 °C (ethyl acetate/hexanes); δ_H(CDCl$_3$) = 8.24 (s, 1H), 7.42 (s, 1H), 7.23 (d, J = 9.0 Hz, 1H), 6.97 (dd, J = 9.2, 2.6 Hz, 1H), 6.90 (d, J = 2.7 Hz, 1H), 3.83 (s, 3H), 1.54 (s, 9H) ppm; δ_C(CDCl$_3$) = 158.9, 156.8, 152.7, 144.2, 125.2, 120.8, 120.4, 117.5, 116.8, 109.8, 82.0, 56.0, 28.4 ppm; IR ν = 3416 (m), 1729 (s), 1693 (b), 1583 (s), 1488 (m), 1464 (s), 1396 (s), 1362 (m), 1342 (s), 1288 (s), 1230 (b), 1151 (b), 1026 (b), 1011 (b) cm^{-1}; MS *m/z*

(relative intensity) = M$^+$ not observed, 191 (100), 163 (32), 120 (46), 93 (33), 65 (55), 51 (16). HRMS [M$^+$] calcd for C$_{15}$H$_{17}$NO$_5$ 291.1107, found 291.1101.

(7-Methoxy-2-oxo-2*H*-chromen-3-yl)carbamic acid *t*-butyl ester (6f)

6f
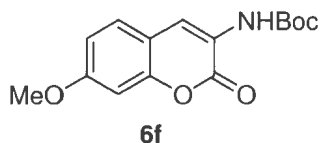
According to representative procedure B, **5f** (0.59 g, 2.6 mmol), DMAP (0.06 g, 0.5 mmol), di-*t*-butyl dicarbonate (2.29 g, 10.5 mmol) and hydrazine hydrate (0.61 mL, 13 mmol) afforded **6f** as a white solid (0.43 g, 58%). mp = 117-118 °C (ethyl acetate/hexanes); δ_H(CDCl$_3$) = 8.23 (s, 1H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.29 (s, 1H), 6.86 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.81 (d, *J* = 1.8 Hz, 1H), 3.85 (s, 3H), 1.53 (s, 9H) ppm; δ_C(CDCl$_3$) = 161.0, 159.1, 152.8, 151.2, 128.3, 122.4, 121.4, 113.5, 113.2, 100.9, 81.7, 55.9, 28.4 ppm; IR ν = 3318 (m), 1726 (m), 1699 (s), 1631 (m), 1613 (s), 1575 (m), 1524 (s), 1454 (s), 1364 (s), 1329 (s), 1295 (s), 1279 (s), 1250 (m), 1226 (s), 1203 (s), 1183 (b), 1152 (s), 1133 (b), 1033 (s), 1013 (s) cm^{-1}; MS *m/z* (relative intensity) = M$^+$ not observed, 191 (100), 148 (21), 130 (7), 77 (3). HRMS [M$^+$] calcd for C$_{15}$H$_{17}$NO$_5$ 291.1107, found 291.1099.

(8-Methoxy-2-oxo-2*H*-chromen-3-yl)carbamic acid *t*-butyl ester (6g)

6g
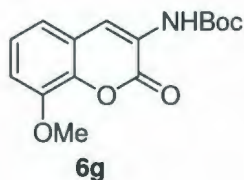
According to representative procedure B, **5g** (4.45 g, 19.1 mmol), DMAP (0.47 g, 3.8 mmol), di-*t*-butyl dicarbonate (17.41 g, 79.75 mmol) and hydrazine hydrate (4.64 mL, 95.4 mmol) afforded **6g** as a white solid (5.10 g, 92%). mp = 97-99 °C (ethyl acetate/hexanes); δ_H(CDCl$_3$) = 8.25 (s, 1H), 7.43 (s, 1H), 7.22-7.19 (m, 1H), 7.04 (d, J = 7.0 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 3.96 (s, 3H), 1.53 (s, 9H) ppm; δ_C(CDCl$_3$) = 158.3, 152.7, 147.2, 139.2, 125.1, 125.1, 121.0, 120.6, 119.1, 111.3, 81.9, 56.4, 28.4 ppm; IR ν = 3318 (m), 1729 (s), 1703 (s), 1580 (m), 1532 (m), 1477 (m), 1395 (s), 1362 (s), 1276 (s), 1239 (s), 1186 (m), 1156 (m), 1112 (s), 1077 (m), 1040 (m), 1013 (m) cm^{-1}; MS *m/z* (relative intensity) = M$^+$ not observed, 191 (100), 163 (31), 136 (22), 120 (30), 106 (16), 93 (35), 76 (20), 65 (56), 51 (16). HRMS [M$^+$] calcd for C$_{15}$H$_{17}$NO$_5$ 291.1107, found 291.1110.

(7-Hydroxy-2-oxo-2*H*-chromen-3-yl)carbamic acid *t*-butyl ester (6h)
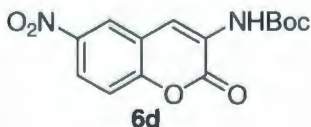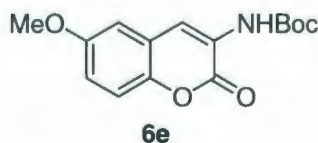

6h
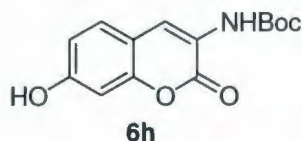
According to representative procedure B, **5h** (2.83 g, 10.8 mmol), DMAP (0.26 g, 2.2 mmol), di-*t*-butyl dicarbonate (10.56 g, 45.27 mmol) and hydrazine hydrate (5.26 mL, 108 mmol) afforded **6h** as a white solid (1.61 g, 50%). mp = 177-178 °C (dichloromethane/hexanes); δ_H(CDCl$_3$) = 8.24 (s, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.27 (s, 1H), 6.88 (d, *J* = 1.5 Hz, 1H), 6.83 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.42 (s, 1H), 1.53 (s, 9H) ppm; δ_C(CDCl$_3$) = 159.6, 157.8, 152.9, 151.1, 128.7, 122.4, 122.0, 114.3, 113.4, 103.2, 82.0, 28.4 ppm; IR ν = 3317 (m), 1703 (s), 1681 (s), 1633 (s), 1608 (s), 1535 (s), 1512 (s), 1453 (b), 1393 (s), 1367 (s), 1288 (m), 1268 (s), 1244 (s), 1199 (m), 1160 (s), 1124 (b), 1045 (m), 1020 (s) cm^{-1}; MS *m/z* (relative intensity) = M$^+$ not observed, 249 (10), 207 (31), 177 (100), 149 (56), 122 (21), 79 (18), 66 (19). HRMS [M$^+$] calcd for C$_{14}$H$_{15}$NO$_5$ 277.0950, found 277.0951.

(5,6-Benzo-2-oxo-2*H*-chromen-3-yl)carbamic acid *t*-butyl ester (6i)

6i
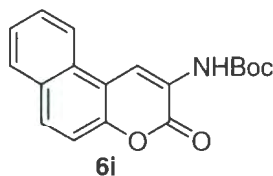
According to representative procedure B, **5i** (0.40 g, 1.6 mmol), DMAP (0.04 g, 0.3 mmol), di-*t*-butyl dicarbonate (1.37 g, 6.27 mmol) and hydrazine hydrate (0.40 mL, 7.5 mmol) afforded **6i** as a pale yellow solid (0.47 g, 95%). mp = 192-194 °C (ethyl acetate/hexanes); δ_H(CDCl$_3$) = 9.10 (s, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 7.90-7.85 (m, 2H), 7.65-7.64 (m, 1H), 7.58-7.55 (m, 1H), 7.49 (s, 1H), 7.44 (d, *J* = 9.4 Hz, 1H), 1.59 (s, 9H) ppm; δ_C(CDCl$_3$) = 158.8, 152.8, 148.3, 130.9, 130.3, 129.2, 129.0, 127.8, 126.3, 124.8, 122.6, 116.8, 116.6, 114.6, 82.0, 28.5; IR ν = 3316 (m), 1701 (s), 1575 (s), 1522 (s), 1461 (m), 1408 (m), 1392 (m), 1367 (m), 1341 (m), 1242 (s), 1153 (s), 1045 (m), 1015 (m) cm^{-1}; MS *m/z* (relative intensity) = M$^+$ not observed, 211 (100), 183 (73), 154 (26), 128 (65), 102 (8), 91 (14), 77 (22), 63 (16). HRMS [M$^+$] calcd for C$_{18}$H$_{17}$NO$_4$ 311.1158, found 311.1149.

3-Amino-6-bromo-2*H*-chromen-2-one (7b)

7b
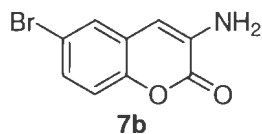
According to representative procedure C, **6b** (1.25 g, 3.65 mmol) afforded **7b** as an off-white solid (0.58 g, 67%). mp = 205-206 °C (ethyl acetate/hexanes) (Lit.[10d] 204-205 °C); δ_H(CDCl$_3$) = 7.42 (d, J = 1.7 Hz, 1H), 7.34 (dd, J = 8.7, 2.0 Hz, 1H), 7.15 (d, J = 9.0 Hz, 1H), 6.58 (s, 1H), 4.36 (s, 2H) ppm; δ_C(CDCl$_3$) = 159.0, 148.0, 133.0, 129.4, 127.5, 123.3, 118.0, 117.6, 109.0 ppm.

3-Amino-6-methyl-2*H*-chromen-2-one (7c)

7c
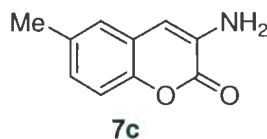
According to representative procedure C, **6c** (3.58 g, 13.0 mmol) afforded **7c** as a brown solid (2.18 g, 96%). mp = 157-159 °C (ethyl acetate/hexanes) (Lit.[10d] 160 °C); δ_H(CDCl$_3$) = 7.17 (d, J = 9.2 Hz, 1H), 7.08-7.07 (m, 2H), 6.65 (s, 1H), 4.20 (s, 2H), 2.37 (s, 3H) ppm; δ_C(CDCl$_3$) = 159.8, 147.4, 134.4, 132.2, 127.8, 125.2, 121.1, 116.1, 111.2, 21.1 ppm.

3-Amino-6-nitro-2*H*-chromen-2-one (7d)

O2N — [chromene structure with NH2, O, O] — 7d
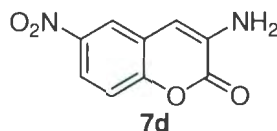
According to representative procedure C, **6d** (0.145 g, 0.500 mmol) afforded **7d** as a yellow solid (0.0892 g, 89%). mp = 200-201 °C (ethyl acetate/hexanes) (Lit.[10] 201-202 °C, Lit.[10] 209 °C); δ_H(CDCl$_3$) = 8.21 (d, *J* = 2.8 Hz, 1H), 8.12 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.39-7.38 (m, 1H), 6.71 (s, 1H), 4.51 (s, 2H) ppm; δ_C(CDCl$_3$) = 158.3, 152.3, 144.8, 133.6, 122.1, 121.5, 120.8, 117.3, 108.4 ppm.

3-Amino-6-methoxy-2*H*-chromen-2-one (7e)

MeO — [chromene structure with NH2, O, O] — 7e
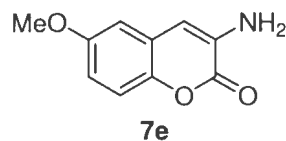
According to representative procedure C, **6e** (0.80 g, 2.8 mmol) afforded **7e** as a pale yellow solid (0.53 g, 95%). mp = 119-121 °C (ethyl acetate/hexanes) (Lit.[16] 120-123 °C); δ_H(CDCl$_3$) = 7.20 (d, *J* = 8.8 Hz, 1H), 6.84 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.74 (d, *J* = 2.5 Hz, 1H), 6.64 (s, 1H), 4.26 (s, 2H), 3.82 (s, 3H) ppm; δ_C(CDCl$_3$) = 159.6, 156.6, 143.7, 132.6, 122.0, 117.2, 114.0, 110.8, 108.1, 55.9 ppm.

3-Amino-7-methoxy-2*H*-chromen-2-one (7f)

7f
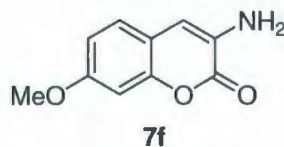
According to representative procedure C, **6f** (0.55 g, 1.9 mmol) afforded **7f** as an off-white solid (0.21 g, 58%) (starting material **3f** (0.20 g, 37%) was recovered). mp = 137-139 °C (ethyl acetate/hexanes) (Lit.[10l] 140-141 °C, Lit.[10d] 154 °C); δ_H(CDCl$_3$) = 7.20 (d, *J* = 9.4 Hz, 1H), 6.82-6.81 (m, 2H), 6.70 (s, 1H), 4.05 (s, 2H), 3.84 (s, 3H) ppm; δ_C(CDCl$_3$) = 159.9, 159.2, 150.5, 129.9, 126.0, 114.6, 112.7, 112.4, 100.9, 55.8 ppm.

3-Amino-8-methoxy-2*H*-chromen-2-one (7g)

7g
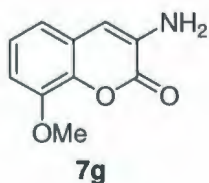
According to representative procedure C, **6g** (0.29 g, 1.0 mmol) afforded **7g** as a brown solid (0.15 g, 80%). mp = 124-125 °C (ethyl acetate/hexanes) (Lit.[10l] 124 °C -126 °C); δ_H(CDCl$_3$) = 7.13 (s, 1H), 6.87-6.86 (m, 2H), 6.68 (s, 1H), 4.27 (s, 2H), 3.95 (s, 3H)

ppm; δ_C(CDCl$_3$) = 159.1, 147.2, 138.7, 132.5, 124.7, 122.2, 117.2, 111.1, 109.3, 56.4 ppm.

3-Amino-7-hydroxy-2H-chromen-2-one (7h)

7h
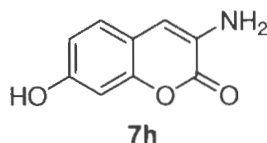
According to representative procedure C, **6h** (0.53 g, 1.9 mmol) afforded **7h** as a light brown solid (0.33 g, 96%). mp = 237-238 °C (ethyl acetate/hexanes) (Lit.[6a] 250 °C); δ_H(DMSO-d_6) = 9.82 (s, 1H), 7.24 (d, J = 8.5 Hz, 1H), 6.72-6.66 (m, 3H), 3.69 (s, 2H) ppm; δ_C(DMSO-d_6) = 159.3, 156.4, 149.6, 130.3, 126.1, 113.7, 113.3, 110.5, 102.1 ppm; IR ν = 3348 (m), 1726 (m), 1681 (s), 1614 (b), 1561 (s), 1509 (s), 1458 (m), 1417 (s), 1360 (m), 1288 (s), 1259 (s), 1242 (m), 1198 (m), 1166 (s), 1153 (s), 1128 (s) cm^{-1}; MS m/z (relative intensity) = 177 (100), 149 (53), 122 (7), 94 (26), 51 (13). HRMS [M$^+$] calcd for C$_9$H$_7$NO$_3$ 177.0426, found 177.0434.

3-Amino-5,6-benzo-2H-chromen-2-one (7i)

**7i**
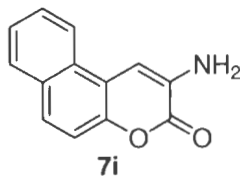
According to representative procedure C, **6i** (5.20 g, 20.5 mmol) afforded **7i** as a brown solid (4.14 g, 65%). mp = 150-152 °C (ethyl acetate/hexanes) (Lit.[10l] 156-158 °C, Lit.[10d] 159 °C); δ_H(CDCl$_3$) = 8.16 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 4.5 Hz, 1H), 7.75 (d, J = 9.5 Hz, 1H), 7.64-7.60 (m, 1H), 7.56-7.53 (m, 1H), 7.50 (s, 1H), 7.45 (d, J = 9.5 Hz, 1H), 4.41 (s, 2H) ppm; δ_C(CDCl$_3$) = 159.5, 147.3, 132.2, 130.9, 129.0, 128.3, 127.6, 127.1, 125.8, 122.0, 116.7, 115.6, 107.6 ppm.

3-Trifluoroacetamido-2*H*-chromen-2-one (8a)

8a
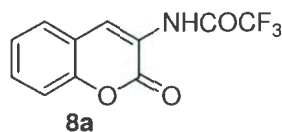
Method 1: According to representative procedure C, **6a** (5.60 g, 21.43 mmol) afforded **8a** as a light brown solid (0.75 g, 14%) after 31 h.

Method 2: A solution of **7a** (0.081 g, 0.50 mmol) in 15% TFA/CHCl$_3$ was stirred at room temperature for 8 d. Then it was refluxed for 24 h. The solvents were removed under reduced pressure and the residue was then chromatographed on silica gel (10% ethyl acetate/hexanes) to afford **8a** as a light brown solid (0.088 g, 68%). mp = 132-133 °C (ethyl acetate/hexanes); δ_H(CDCl$_3$) = 8.81 (s, 1H), 8.70 (s, 1H), 7.59-7.54 (m, 2H), 7.40-7.36 (m, 2H) ppm; δ_C(CDCl$_3$) = 158.1, 155.7 (q, $J_{C\text{-}F}$ = 39.1 Hz), 150.7, 131.3,

34

128.5, 126.5, 125.8, 122.2, 119.0, 116.9, 115.3 (q, J_{C-F} = 288.4 Hz) ppm; IR ν = 3298 (m), 1735 (m), 1694 (s), 1626 (b), 1607 (s), 1555 (s), 1490 (m), 1458 (s), 1381 (m), 1330 (s), 1311 (s), 1189 (m), 1160 (m), 1146 (s), 1090 (s) cm^{-1}; HRMS [M$^+$] calcd for $C_{11}H_6F_3NO_3$ 257.0300, found 257.0298.

3-(2-Hydroxybenzylideneamino)-6-methoxy-2*H*-chromen-2-one (9b)

9b
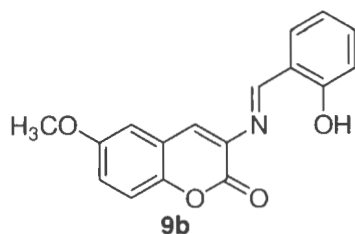
According to representative procedure D, **7e** (0.095 g, 0.50 mmol) and **4a** (0.065 g, 0.53 mmol) afforded **9b** as a bright yellow solid (0.106 g, 72%). mp = 161-163 °C (CHCl$_3$). δ_H(CDCl$_3$) = 12.95 (s, 1H, *OH*), 9.45 (s, 1H), 7.66 (s, 1H), 7.44 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.40 (m, 1H), 7.31 (d, *J* = 9.1 Hz, 1H), 7.20 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 3H, *OCH₃*) ppm; δ_C(CDCl$_3$) = 167.7, 161.9, 158.4, 156.9, 147.1, 134.6, 134.4, 132.4, 120.4, 119.84, 119.78, 119.7, 117.9, 117.8, 110.2, 56.3 (*OCH₃*) ppm (one carbon signal fewer than expected, presumably due to accidental degeneracy); IR: 3450 (w), 1703 (s), 1627 (w), 1592 (w), 1573 (w), 1558 (w), 1495 (m), 1454 (w), 1431 (w), 1400 (w), 1351 (w), 1329 (w), 1313 (w), 1277 (s), 1240 (w) cm^{-1}; MS (APCI) *m/z* (relative intensity) = 297

(M^++2, 21), 296 (M^++1, 100); HRMS [M^+] calcd for $C_{17}H_{13}NO_4$ 295.0845, found 295.0853.

3-(2-Hydroxybenzylideneamino)-6-nitro-2*H*-chromen-2-one (9c)

9c
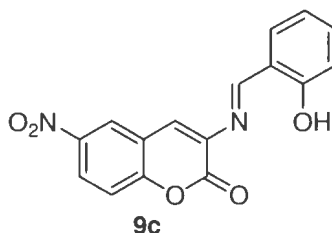
According to representative procedure D, **7d** (0.103 g, 0.50 mmol) and **4a** (0.065 g, 0.53 mmol) afforded **9c** as a yellow solid (0.11 g, 71%). mp = 218-219 °C; δ_H(CDCl$_3$) = 12.57 (s, 1H, *OH*), 9.37 (s, 1H), 8.49 (s, 1H), 8.39 (d, *J* = 7.2 Hz, 1H), 7.72 (s, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.47-7.45 (m, 2H), 7.05 (d, *J* = 7.4 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H) ppm; Due to very low solubility of this compound, ^{13}C NMR could not be obtained in any solvent. IR: 1729 (s), 1642 (w), 1608 (w), 1582 (m), 1540 (w), 1517 (w), 1484 (w), 1441 (w), 1406 (w), 1358 (w), 1310 (m), 1240 (w), 1085 (s) cm^{-1}; MS (APCI) *m/z* (relative intensity) = 312 (M^++2, 20), 311 (M^++1, 100); HRMS [M^+] calcd for $C_{16}H_{10}N_2O_5$ 310.0590, found 310.0584.

3-(2-Hydroxybenzylideneamino)-5,6-benzo-2*H*-chromen-2-one (9d)

9d
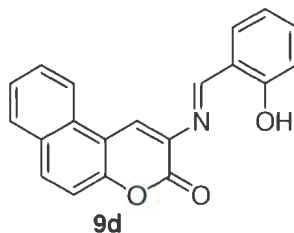
According to representative procedure D, **7i** (0.106 g, 0.50 mmol) and **4a** (0.065 g, 0.53 mmol) affordedh **9d** as an orange solid (0.090 g, 57%). mp = 192-193 °C (CHCl$_3$). δ_H(CDCl$_3$) = 13.08 (s, 1H, *OH*), 9.61 (s, 1H), 8.50 (s, 1H), 8.28 (d, *J* = 7.4 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 7.5 Hz, 1H), 8.21 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.51-7.49 (m, 2H), 7.41-7.40 (m, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H) ppm; δ_C(CDCl$_3$) = 167.3, 161.7, 158.0, 152.0, 134.1, 133.6, 133.2, 131.7, 130.9, 130.7, 129.4, 128.7, 126.6, 122.01, 121.95, 119.6, 117.6, 116.7, 114.2 ppm (one carbon signal fewer than expected, presumably due to accidental degeneracy); IR: 1717 (s), 1683 (w), 1653 (w), 1608 (w), 1575 (m), 1558 (w), 1519 (w), 1508 (w), 1490 (w), 1457 (w), 1437 (w), 1361 (w), 1342 (w), 1278 (m), 1207 (m), 1092 (m), 1063 (s) cm^{-1}; MS (APCI) *m/z* (relative intensity) = 317 (M$^+$+2, 23), 316 (M$^+$+1, 100); HRMS [M$^+$] calcd for C$_{20}$H$_{13}$NO$_3$ 315.0895, found 315.0894.

3-((2-Hydroxynaphthalen-1-yl)methyleneamino)-6-methoxy-2*H*-chromen-2-one (10b)

10b
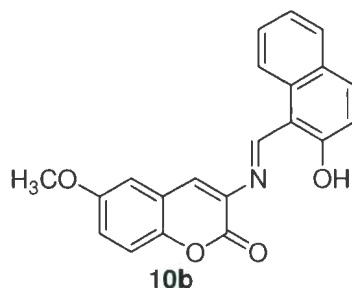
According to representative procedure D, **7e** (0.095 g, 0.50 mmol) and **4i** (0.091 g, 0.53 mmol) afforded **10b** as an orange solid (0.111 g, 64%). mp = 229-230 °C (CHCl$_3$); δ_H(CDCl$_3$) = 15.14 (s, 1H, *OH*), 10.19 (s, 1H), 8.17 (br s, 1H), 7.82 (d, *J* = 9.3 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.64 (br s, 1H), 7.55 (br s, 1H), 7.38-7.36 (m, 2H), 7.31 (d, *J* = 9.6 Hz, 1H), 7.00 (d, *J* = 6.5 Hz, 1H), 6.97 (s, 1H), 3.87 (s, 3H, *OCH$_3$*) ppm; δ_C(CDCl$_3$) = 168.1, 159.5, 158.2, 156.7, 146.6, 137.2, 133.4, 131.3, 131.1, 129.5, 128.5, 127.9, 124.2, 121.3, 120.3, 120.2, 119.9, 117.7, 110.0, 109.9, 56.1 (*OCH$_3$*) ppm; IR: 1710 (s), 1620 (w), 1576 (m), 1543 (m), 1489 (m), 1476 (w), 1460 (w), 1423 (w), 1392 (w), 1328 (m), 1278 (m), 1262 (m), 1231 (w), 1206 (w), 1189 (m, 1168 (w), 1077 (m), 1032 (s) cm^{-1}; MS (APCI) *m/z* (relative intensity) = 347 (M$^+$+2, 23), 345 (M$^+$+1, 100); HRMS [M$^+$] calcd for C$_{21}$H$_{15}$NO$_4$ 345.1001, found 345.1005.

3-((2-Hydroxynaphthalen-1-yl)methyleneamino)-6-nitro-2*H*-chromen-2-one (10c)
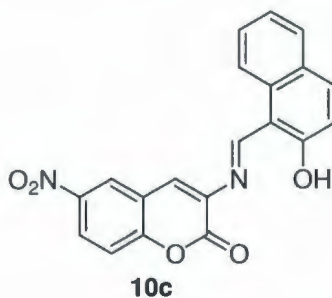
10c

According to representative procedure D, **7i** (0.106 g, 0.50 mmol) and **4i** (0.091 g, 0.53 mmol) afforded **10c** as an orange solid (0.124 g, 68%). mp = 243-245 °C. Due to very low solubility of this compound, NMR spectra could not be obtained in any solvent. IR: 1729 (s), 1642 (w), 1608 (w), 1582 (m), 1540 (w), 1517 (w), 1484 (w), 1441 (w), 1406 (w), 1358 (w), 1310 (m), 1240 (w), 1085 (s) cm^{-1} MS (APCI) *m/z* (relative intensity) = 362 (M$^+$+2, 22), 361 (M$^+$+1, 100); HRMS [M$^+$] calcd for $C_{20}H_{12}N_2O_5$ 360.0746, found 360.0742.

3-((2-Hydroxynaphthalen-1-yl)methyleneamino)-5,6-benzo-2*H*-chromen-2-one (10d)
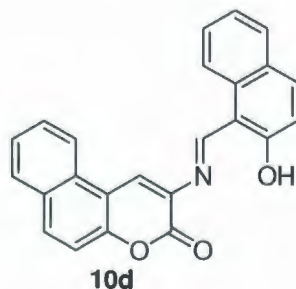
10d

According to representative procedure D, **7i** (0.106 g, 0.50 mmol) and **4i** (0.091 g, 0.53 mmol) afforded **10d** as an orange solid (0.127 g, 70%). mp = 238-240 °C (CHCl$_3$). δ_H(CDCl$_3$) = 15.52 (s, 1H, *OH*), 10.46 (s, 1H), 8.49 (s, 1H), 8.32 (d, *J* = 8.6 Hz, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 8.6 Hz, 1H), 7.76-7.73 (m, 2H), 7.63-7.57 (m, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 9.1 Hz, 1H) ppm; δ_C(CDCl$_3$) = 166.8, 160.5, 158.1, 151.7, 149.8, 136.9, 133.5, 132.8, 130.8, 129.5, 129.4, 129.3, 128.6, 128.0, 126.59, 126.57, 124.2, 122.0, 121.9, 121.0, 120.2, 116.7, 114.3, 110.7 ppm; IR: 1722 (s), 1616 (w), 1600 (w), 1574 (m), 1535 (w), 1508 (w), 1470 (w), 1441 (w), 1377 (w), 1325 (m), 1284 (m), 1246 (w), 1211 (w), 1175 (m), 1160 (w), 1142 (w), 1090 (w), 1057 (s), 1032 (m) cm^{-1}; MS (APCI) *m/z* (relative intensity) = 367 (M$^+$+2, 20), 366 (M$^+$+1, 100); HRMS [M$^+$] calcd for C$_{24}$H$_{15}$NO$_3$ 365.1052, found 365.1049.

1.5 References

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1.6 Appendix

5a

Br —[structure]— NHAc

5b

5c

5d

48

MeO

NHAc

O O

5e

5f

5g

5h

5i

6a

6b

6c

56

6d

=

6e

6f

59

6g

6h

6i

7a

7b

7c

7d

MeO
NH2
7e

7f

7g

7h

70

7i

8

9b

9d

10b

10d
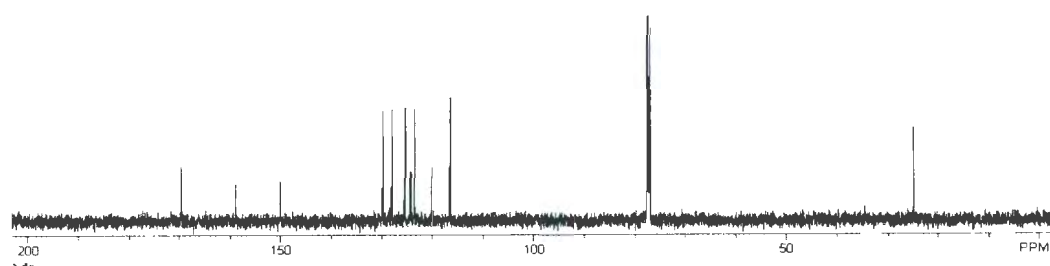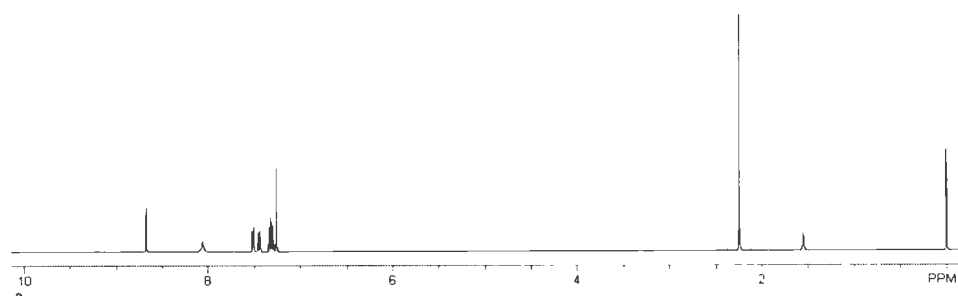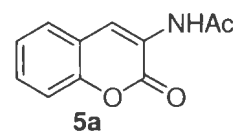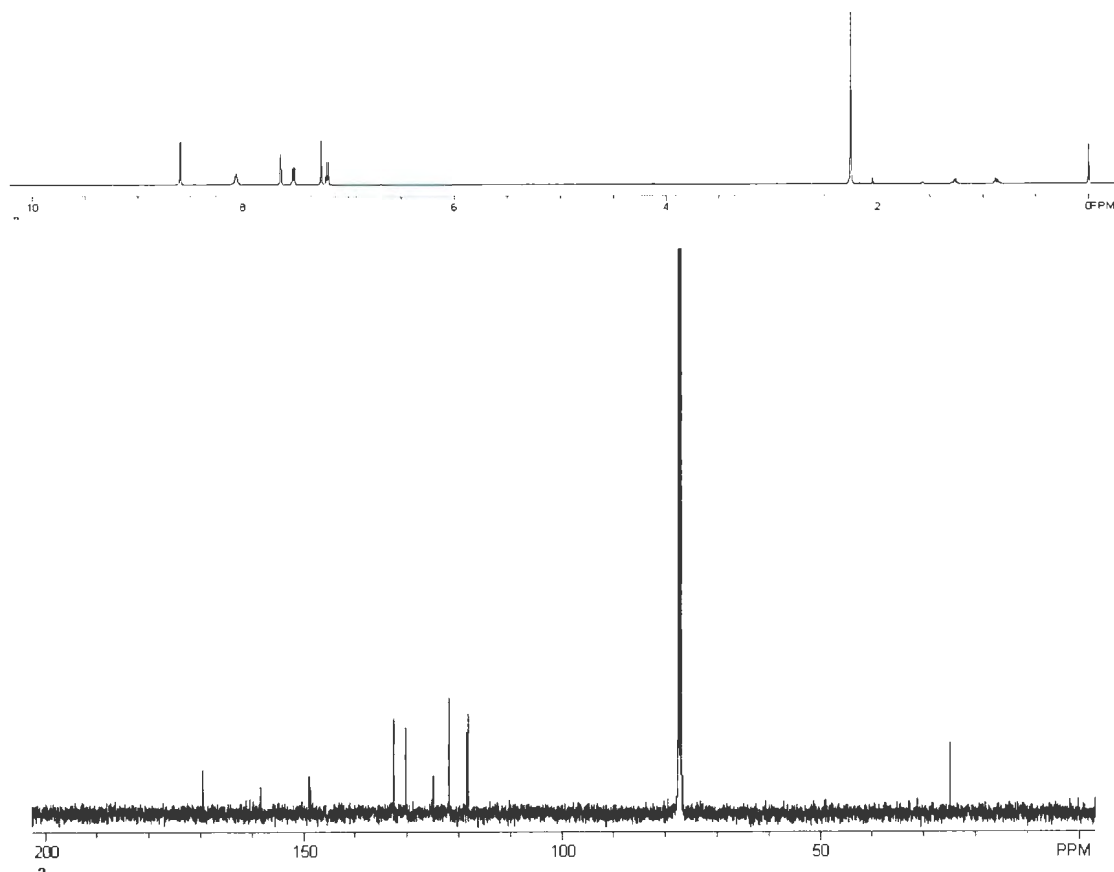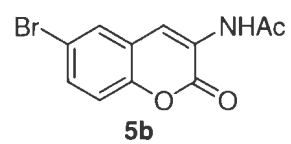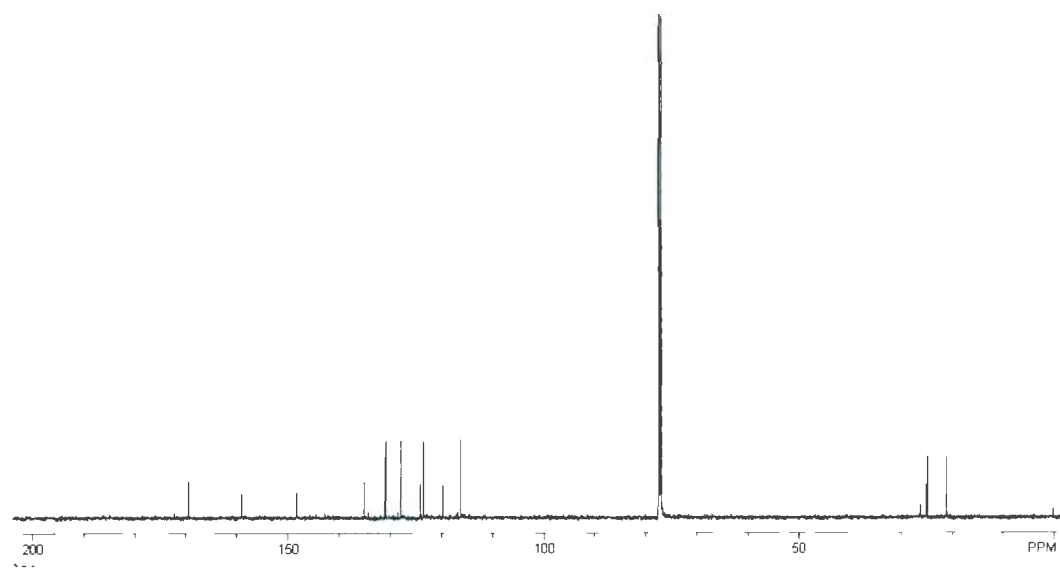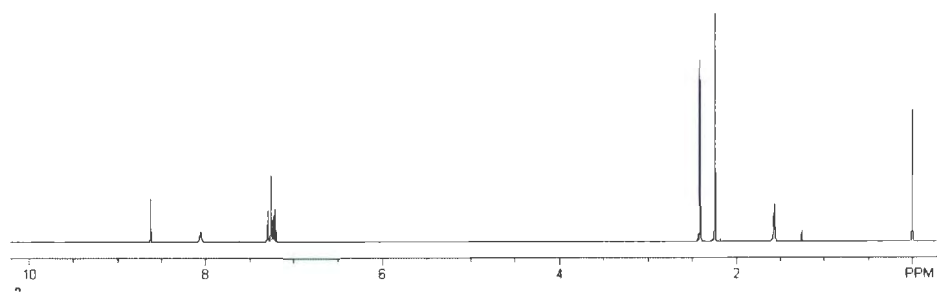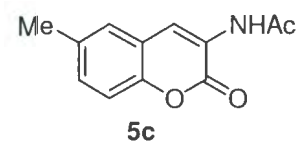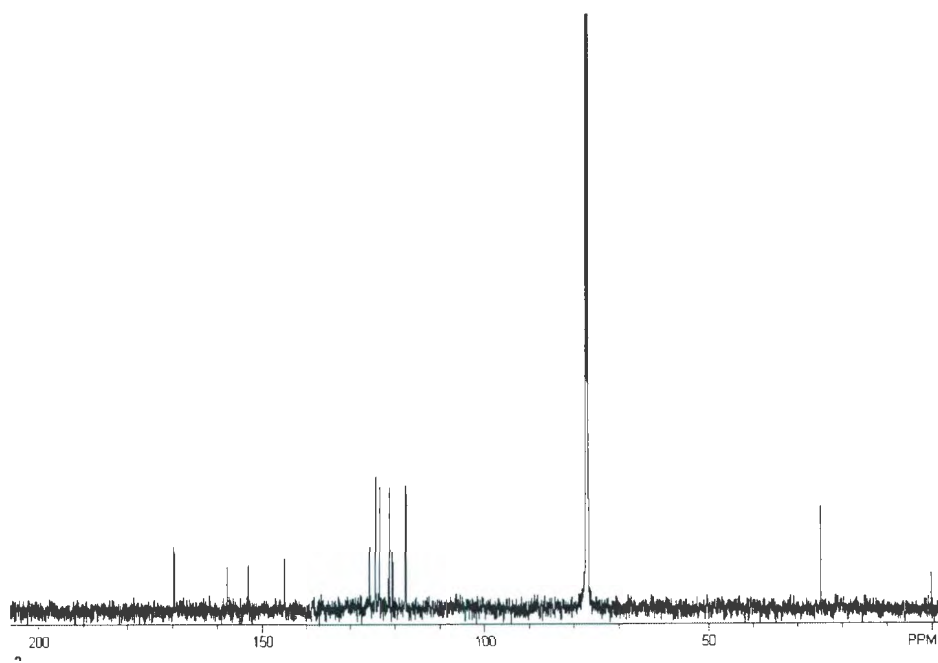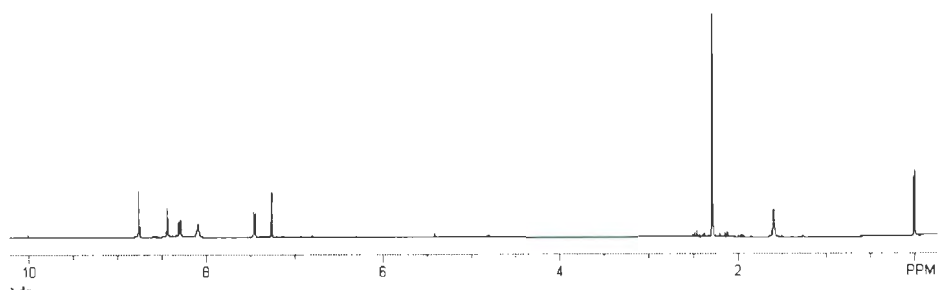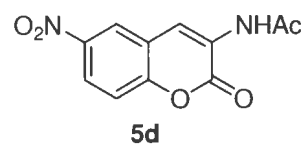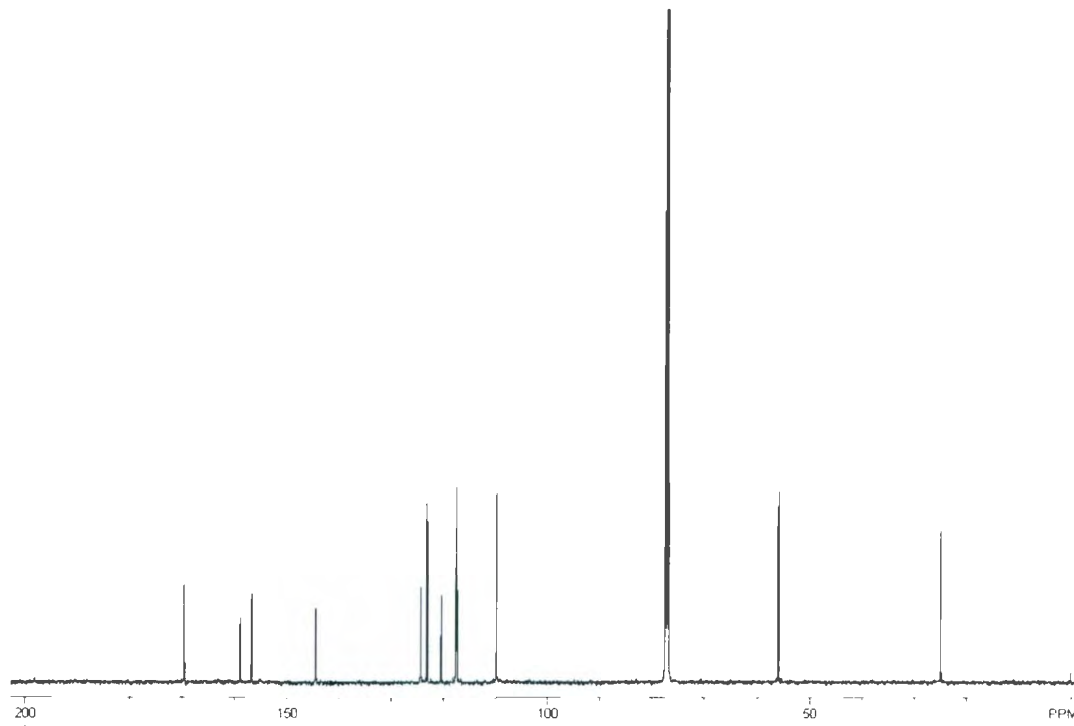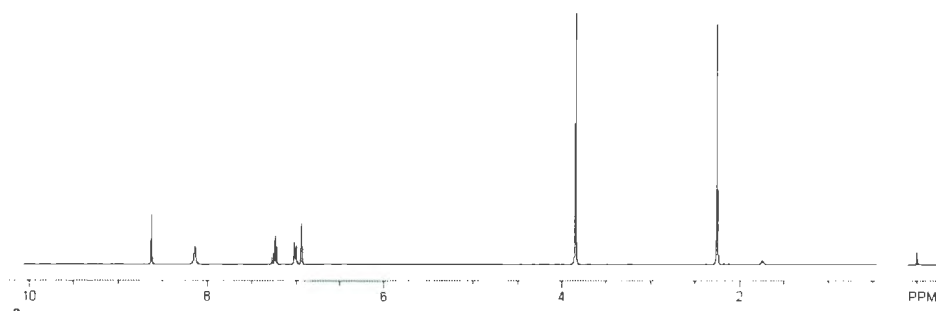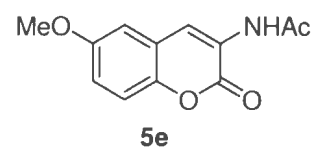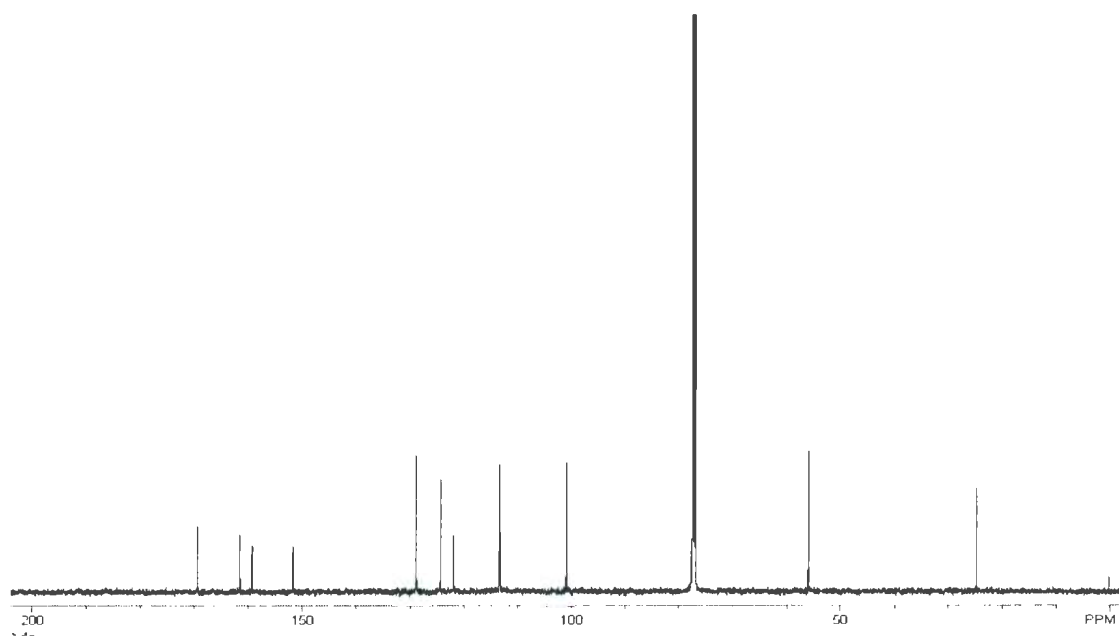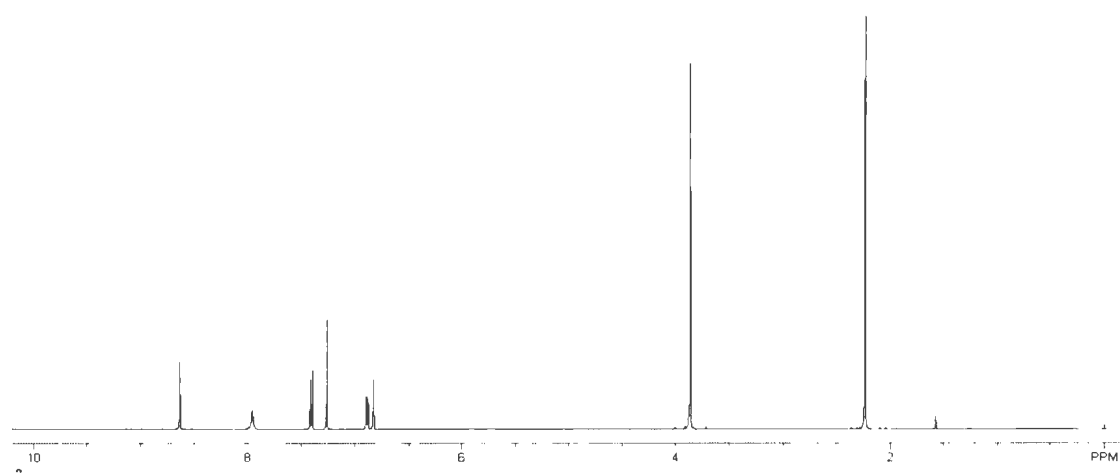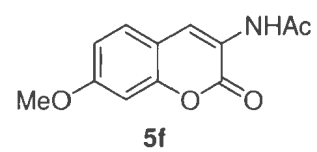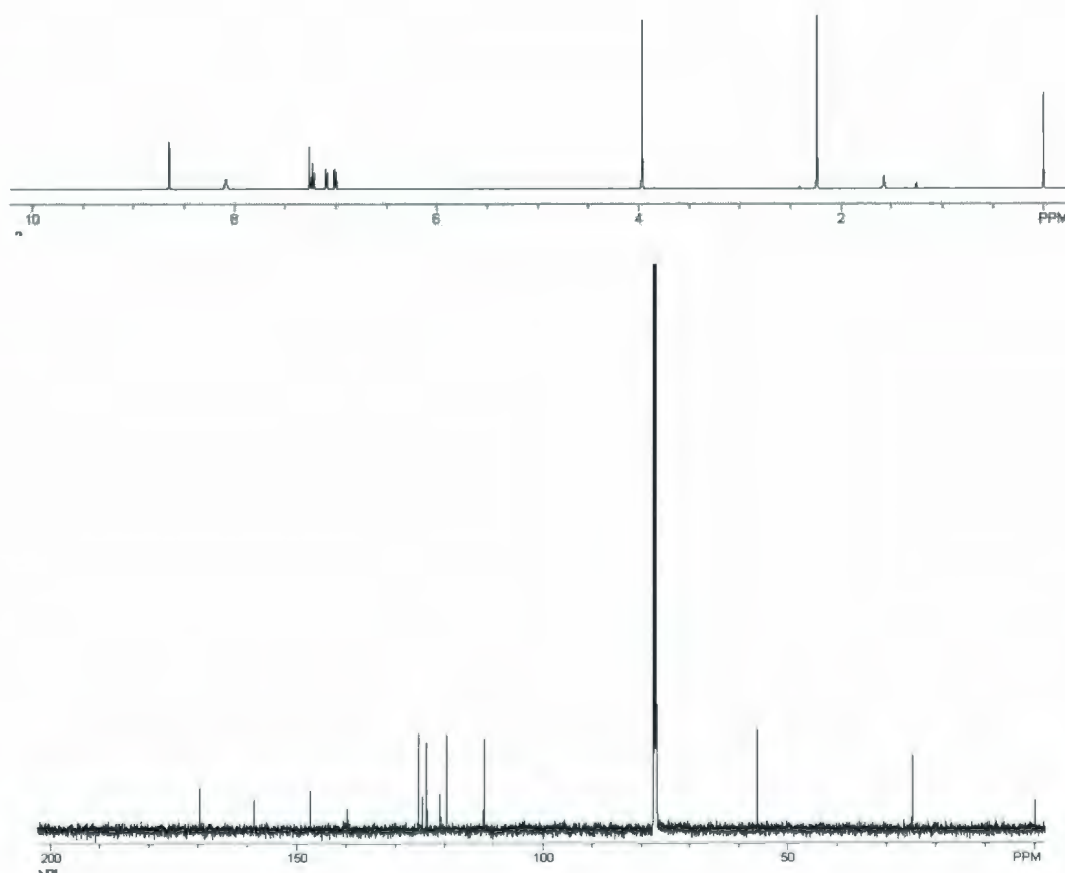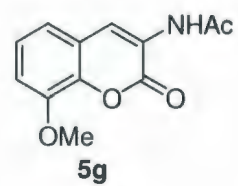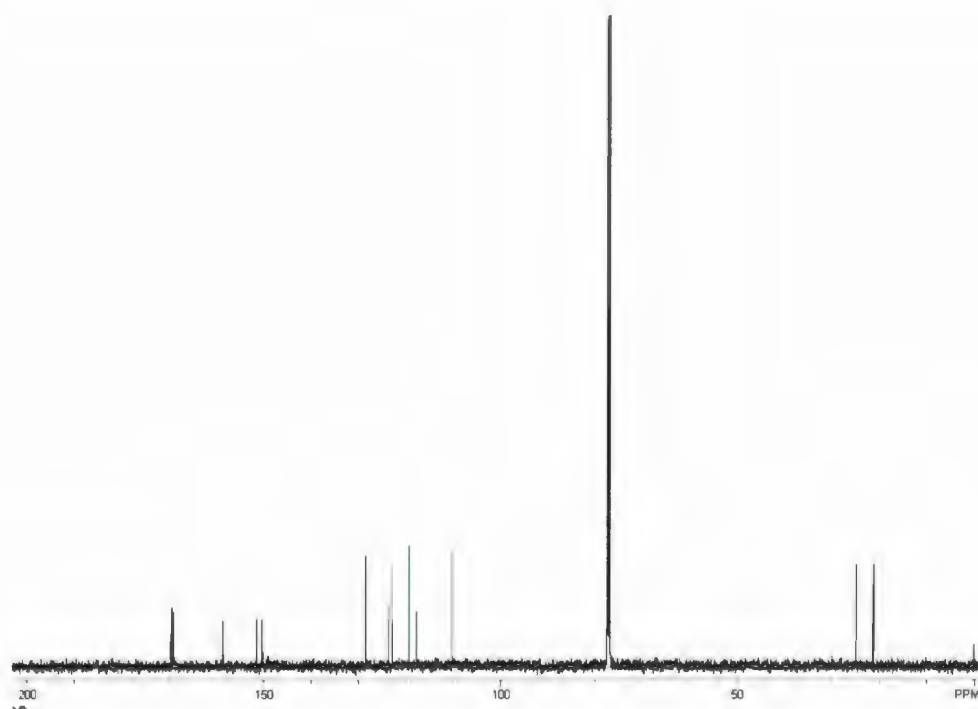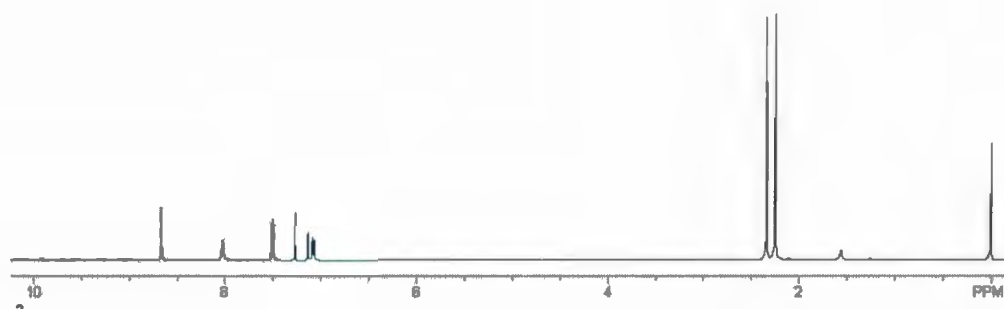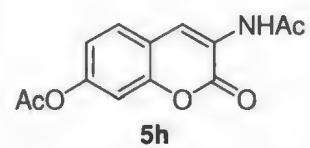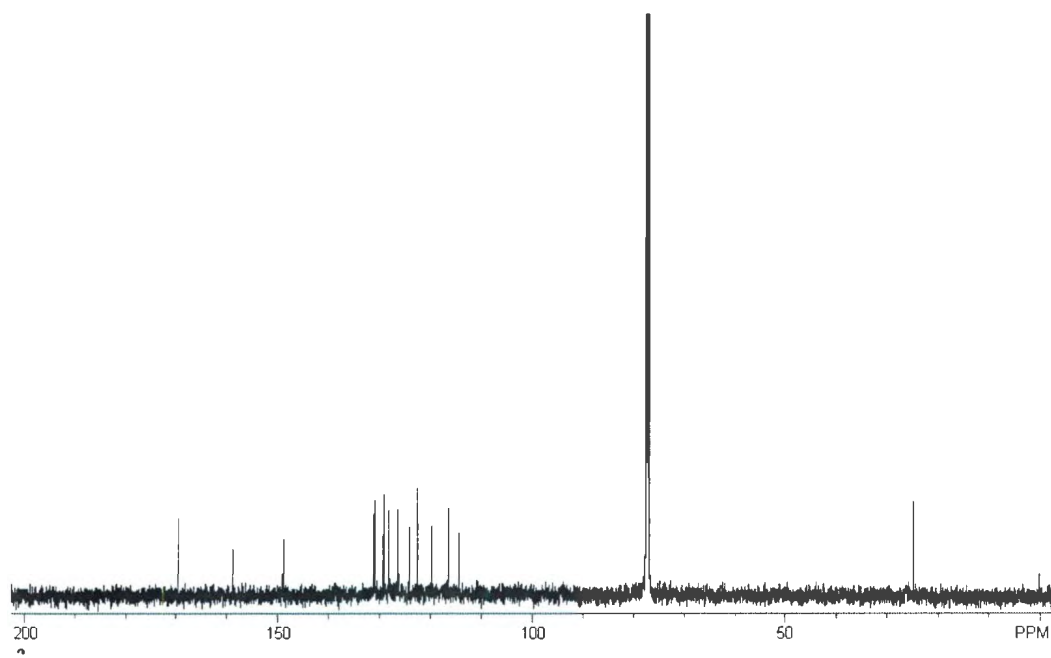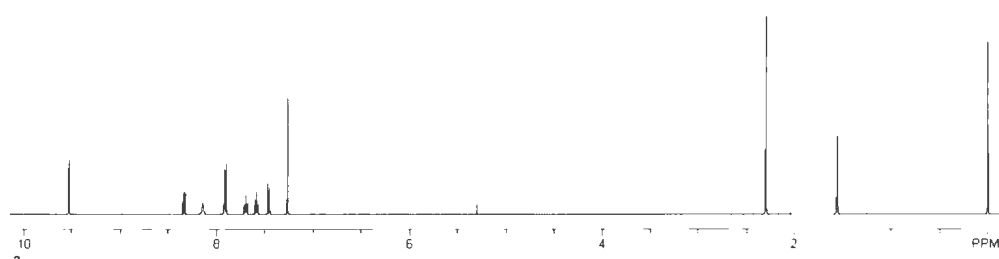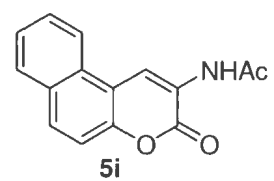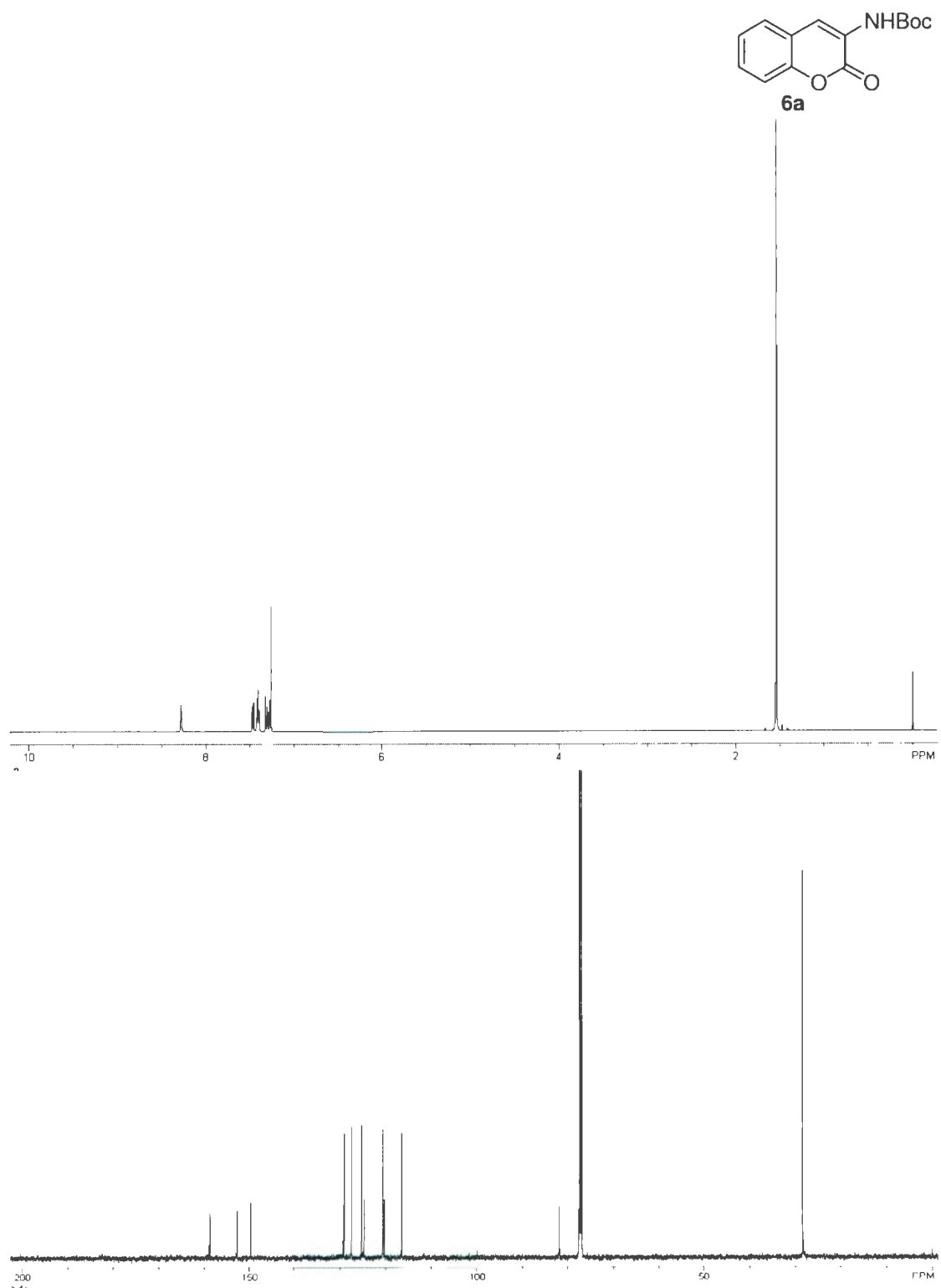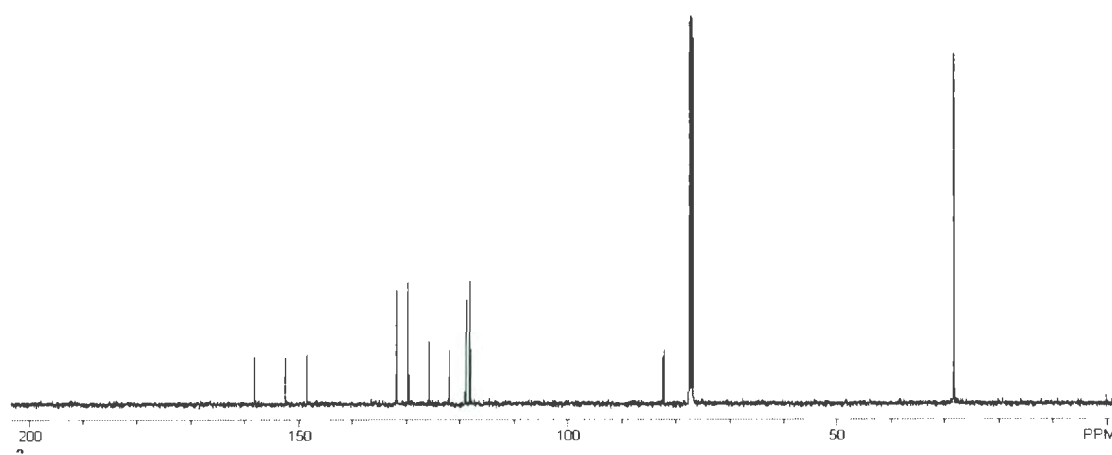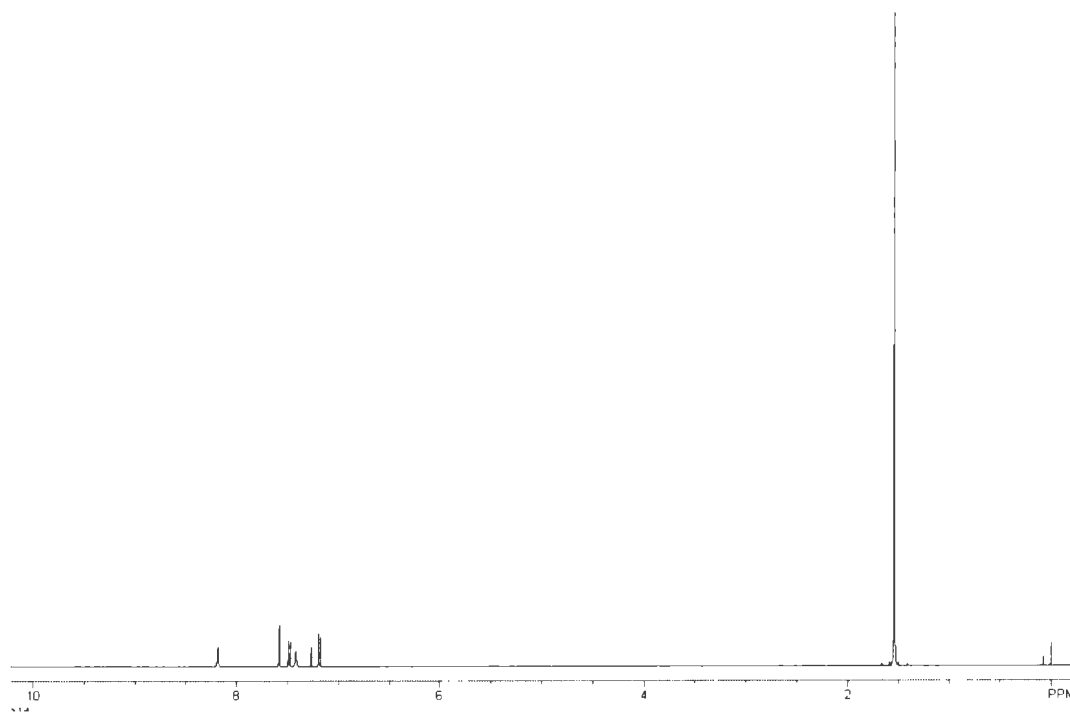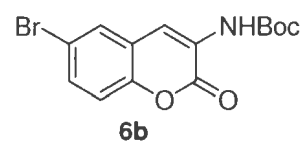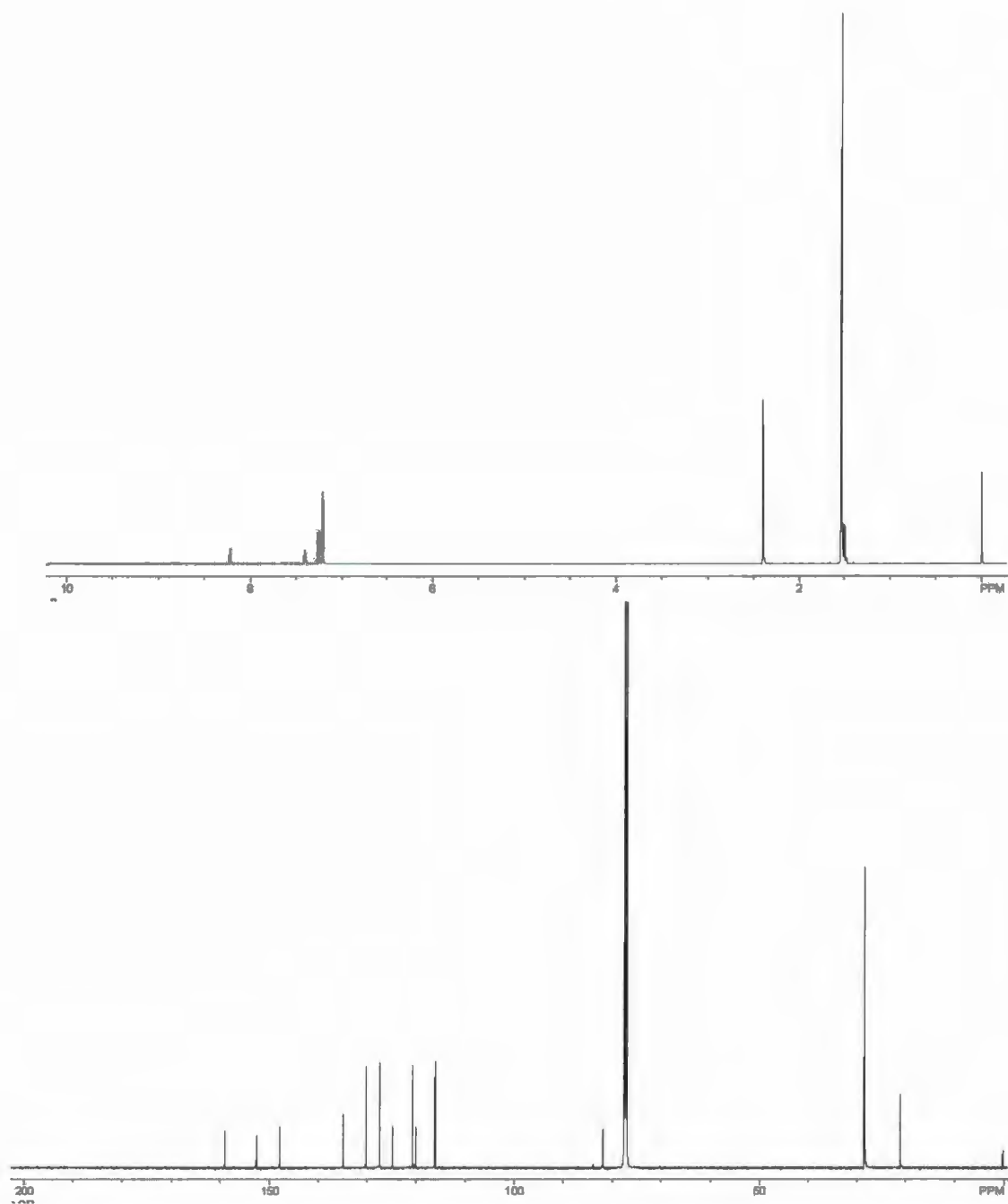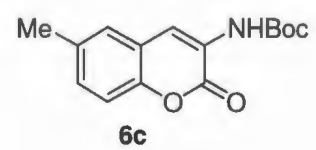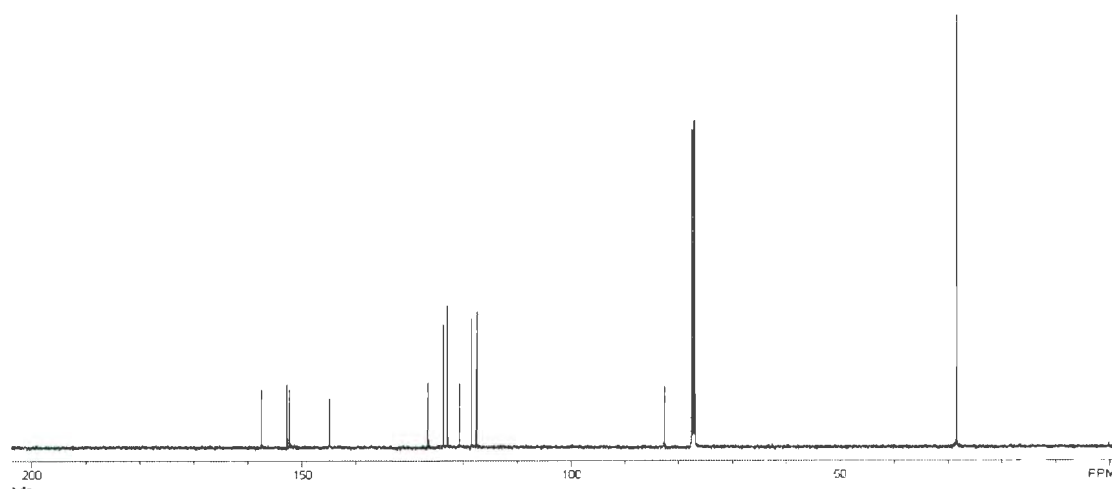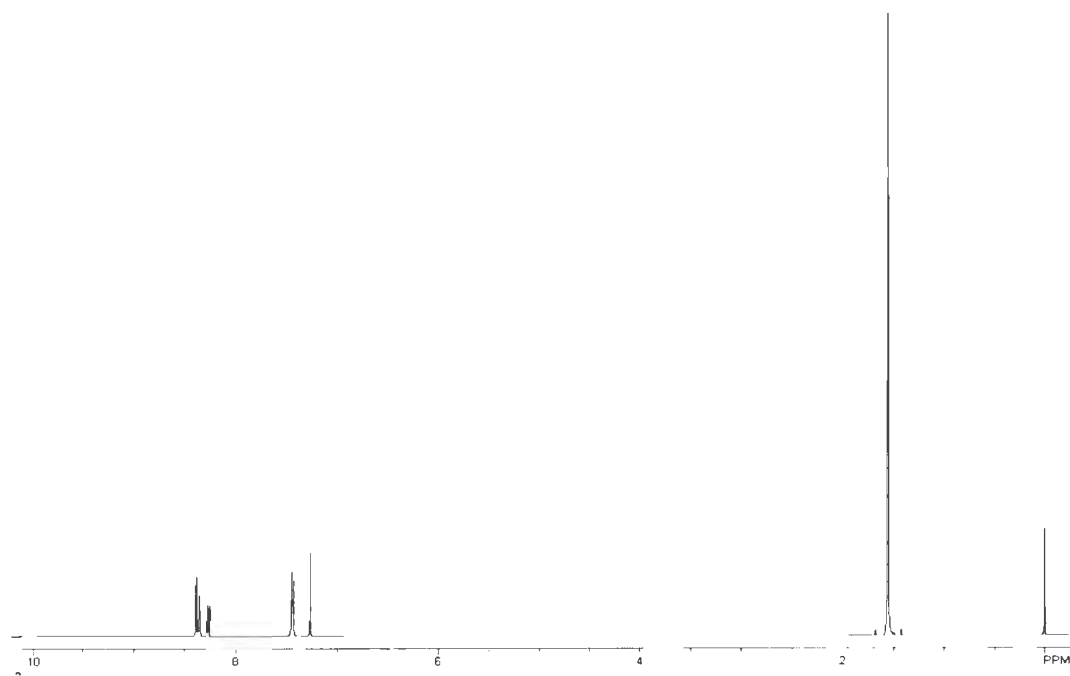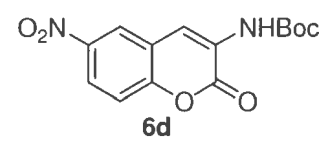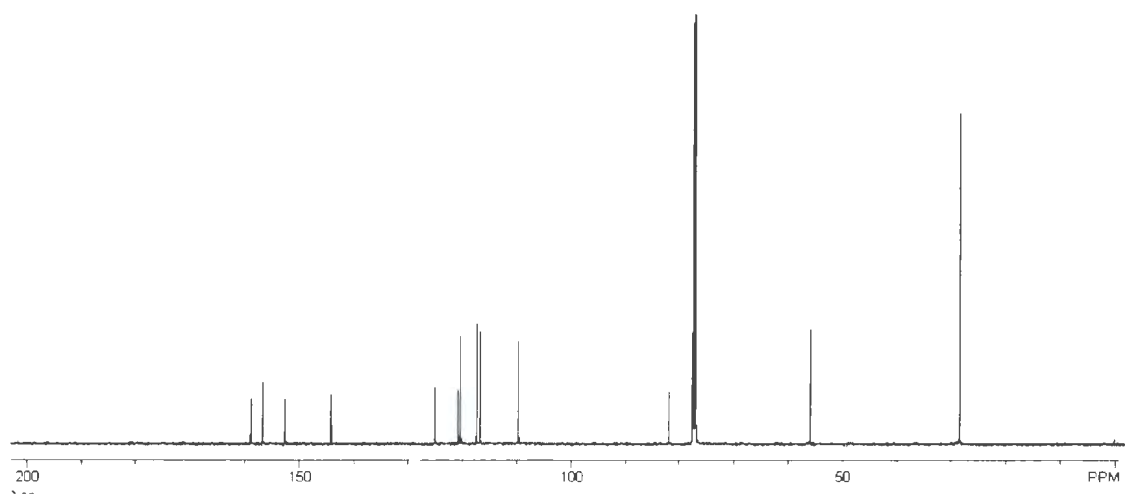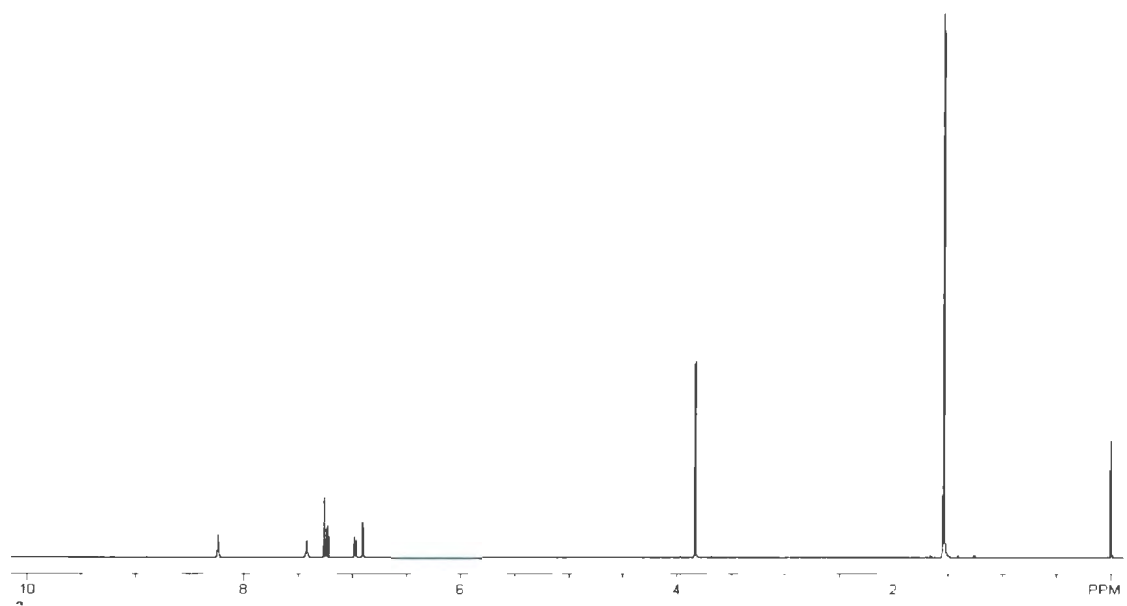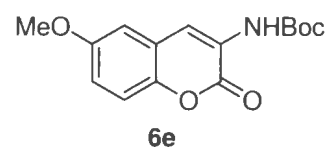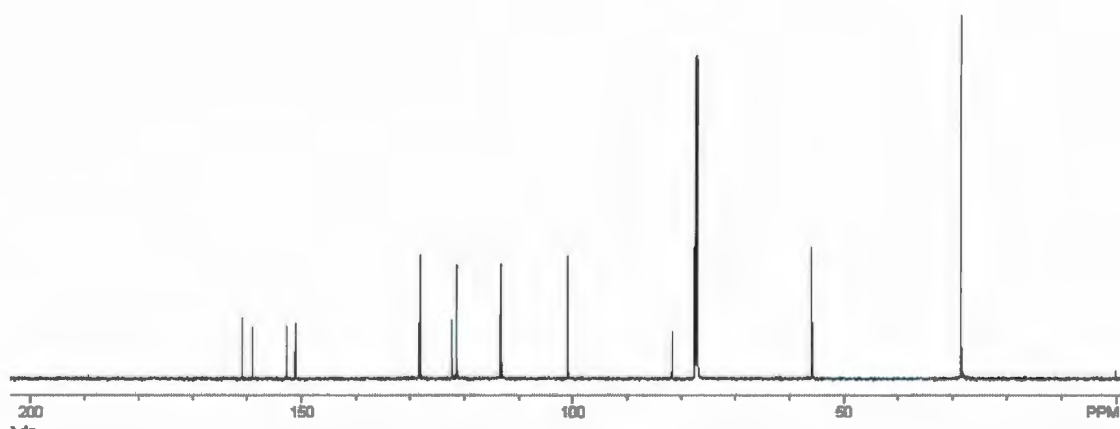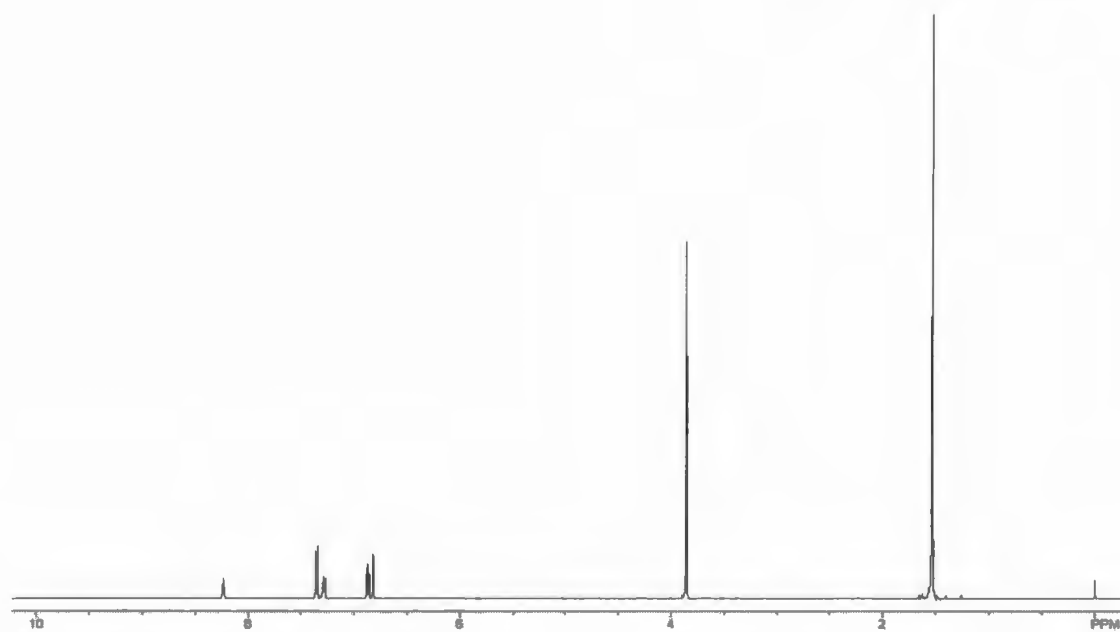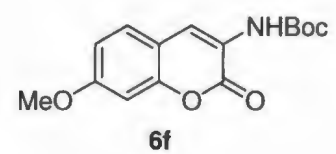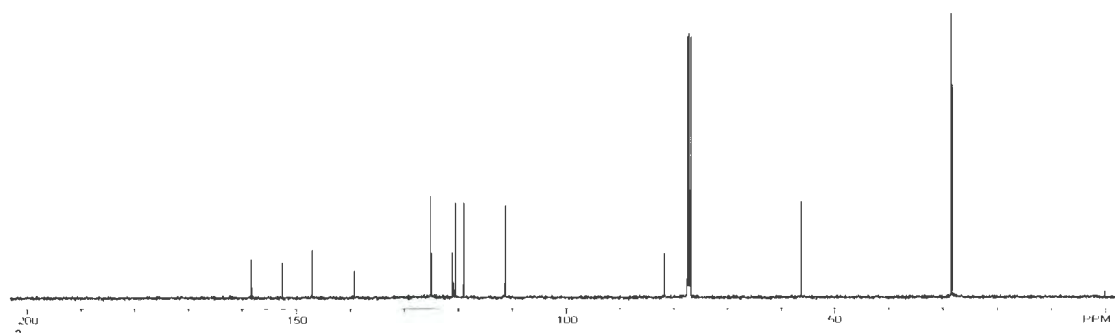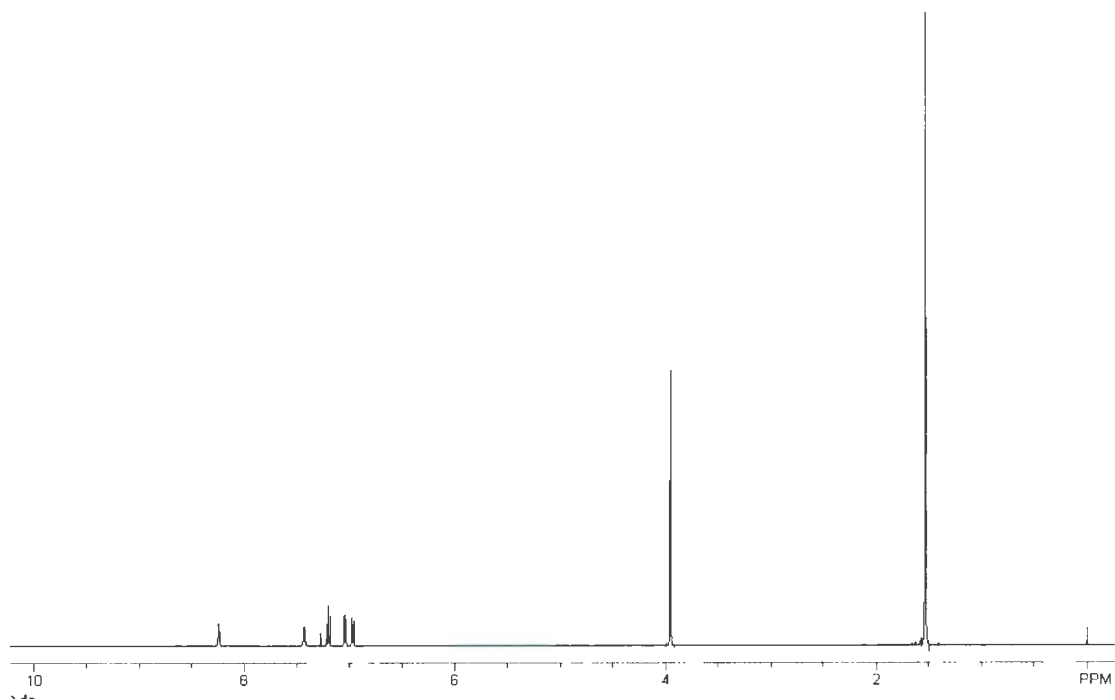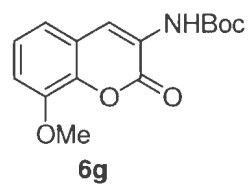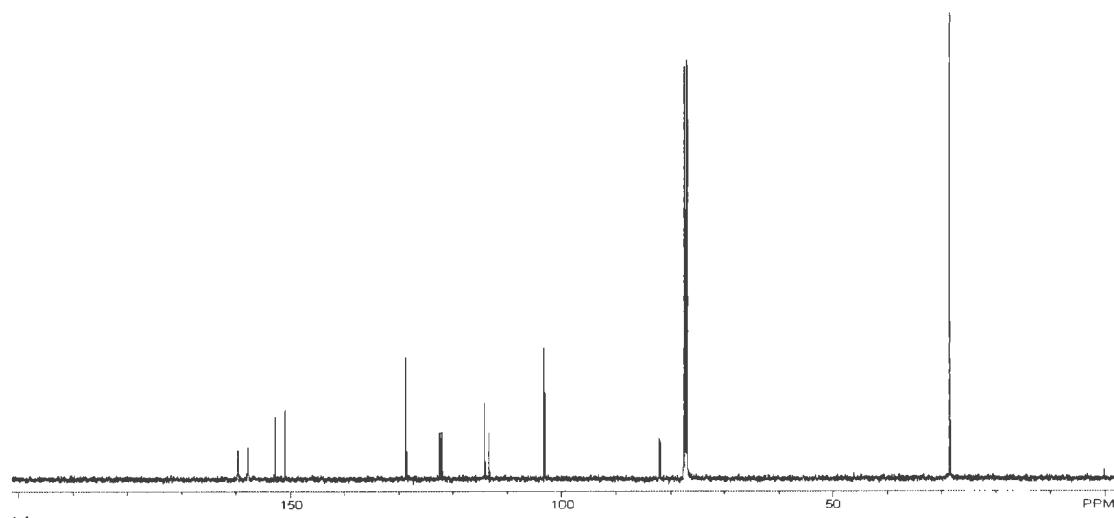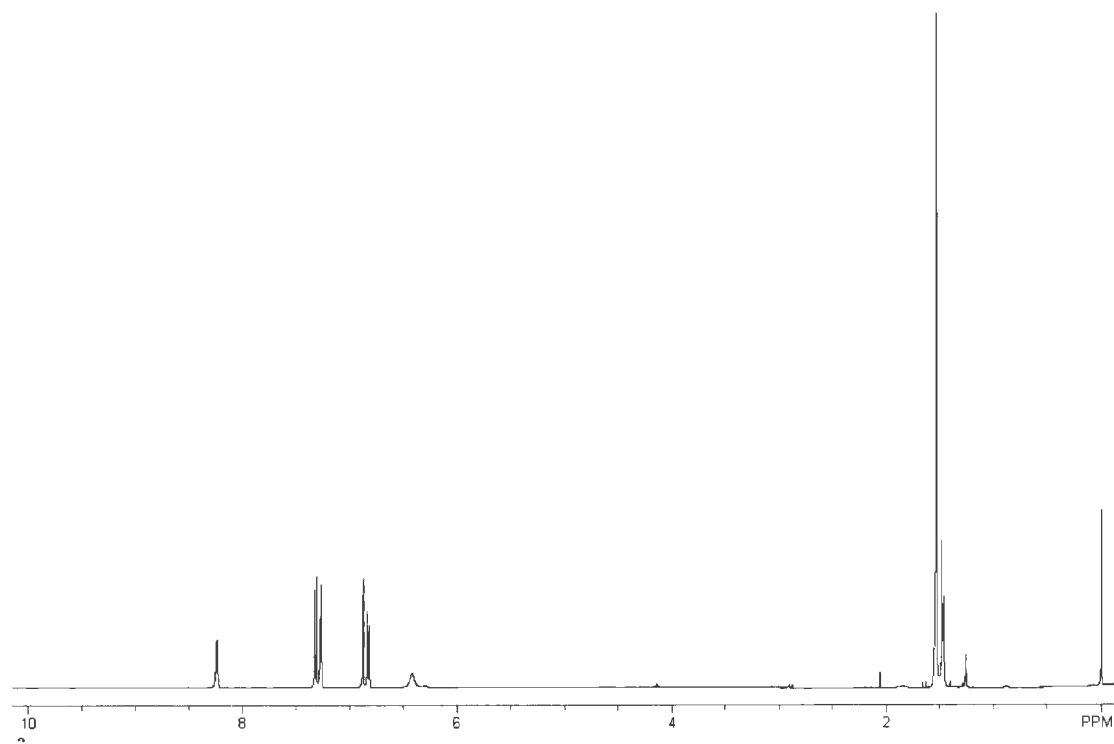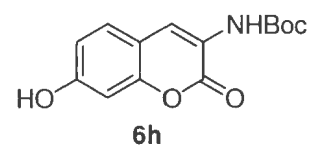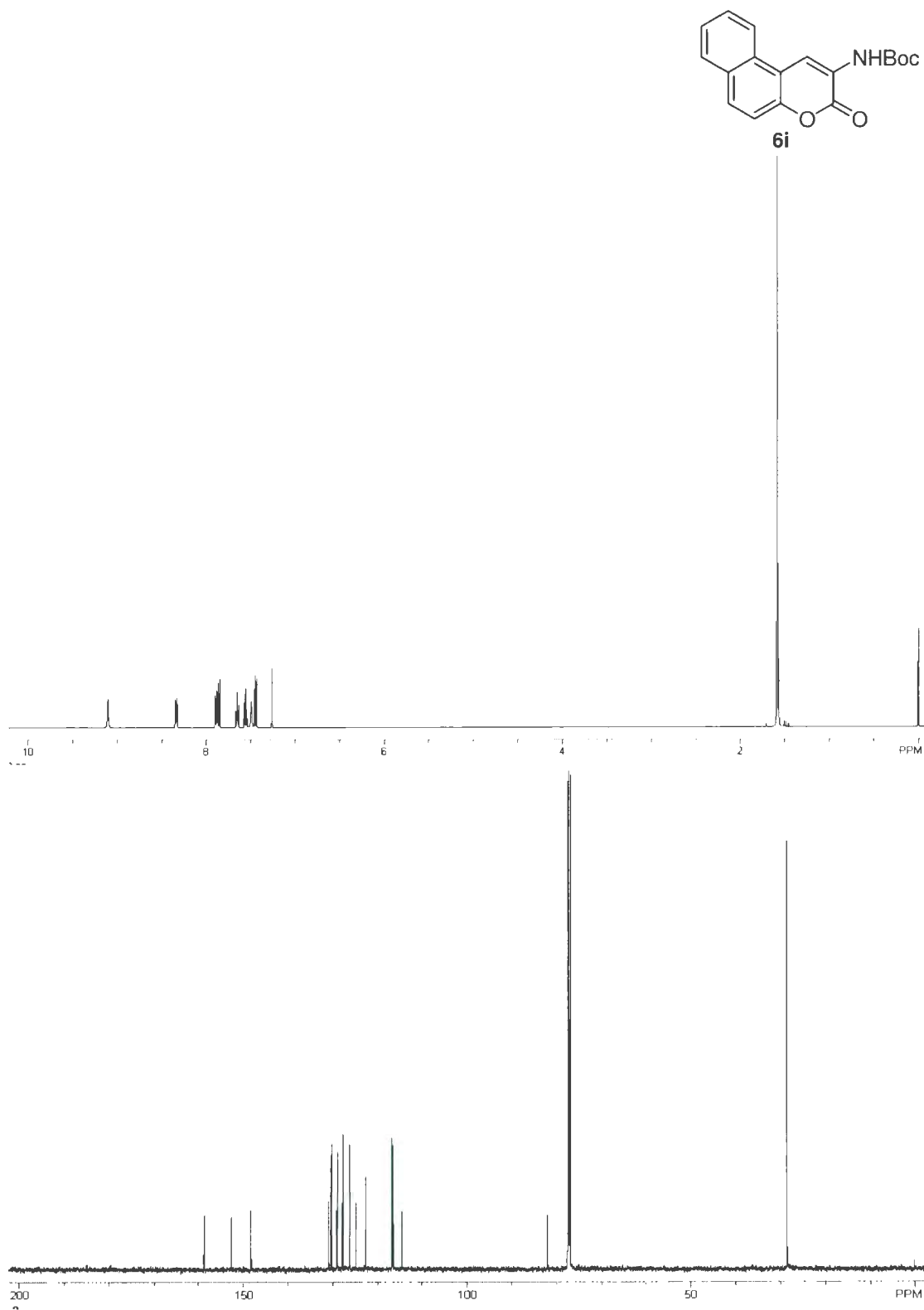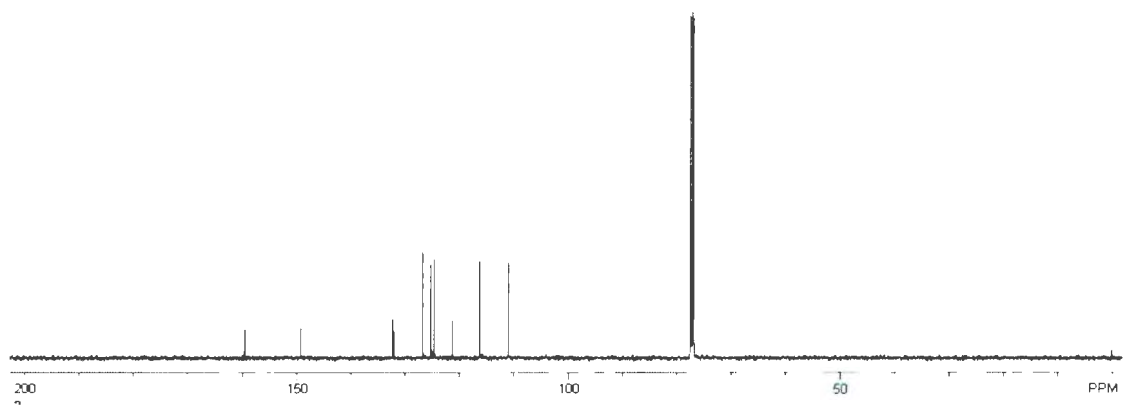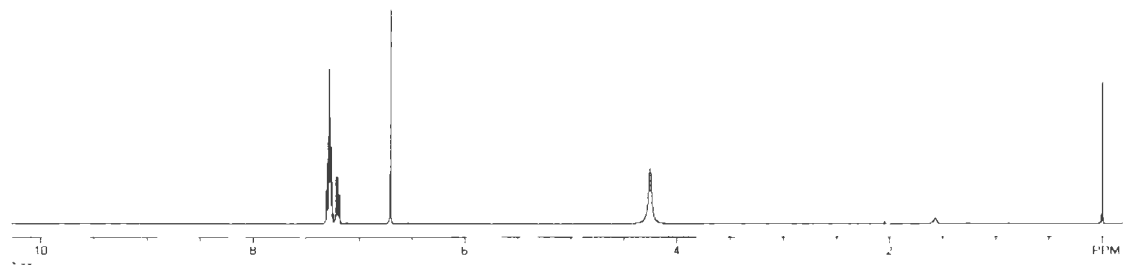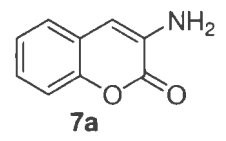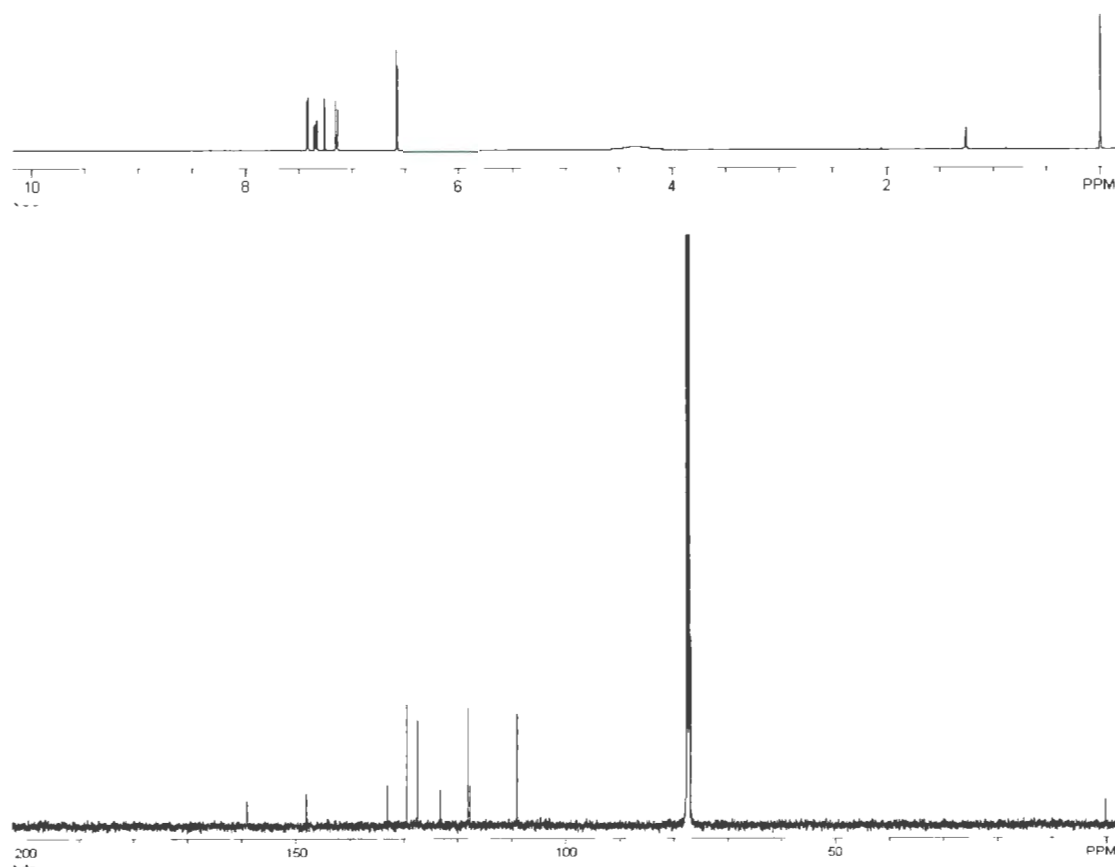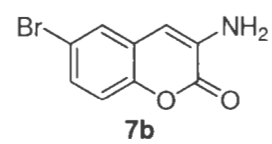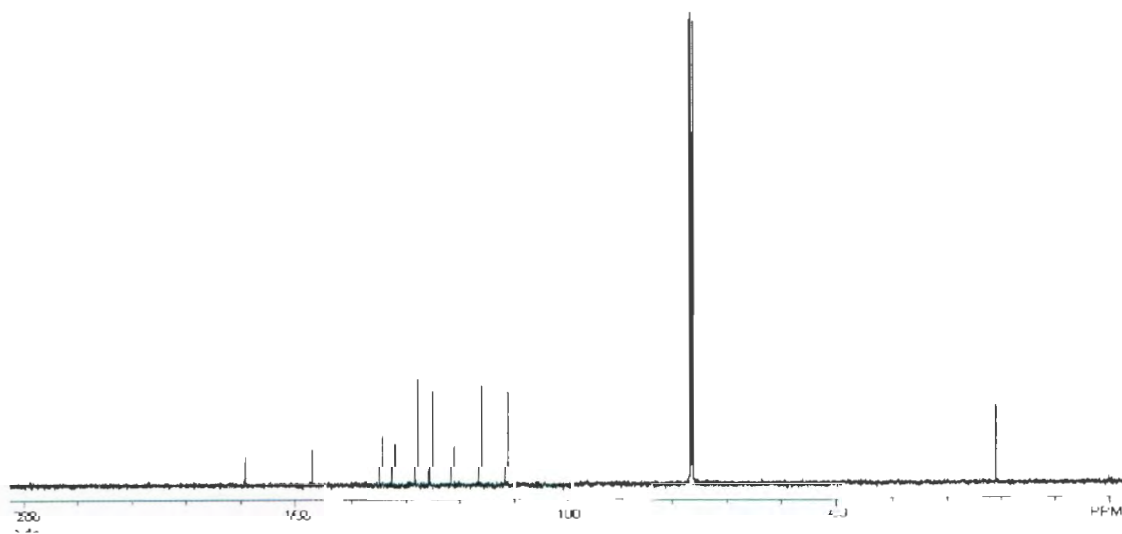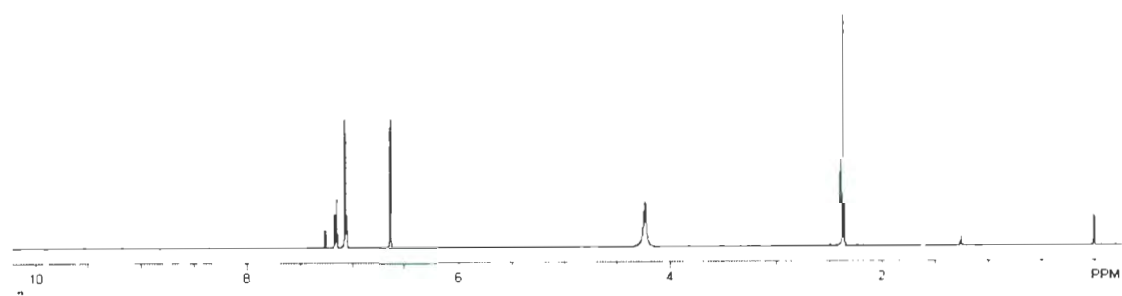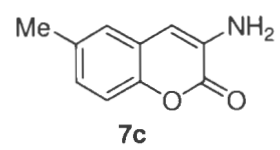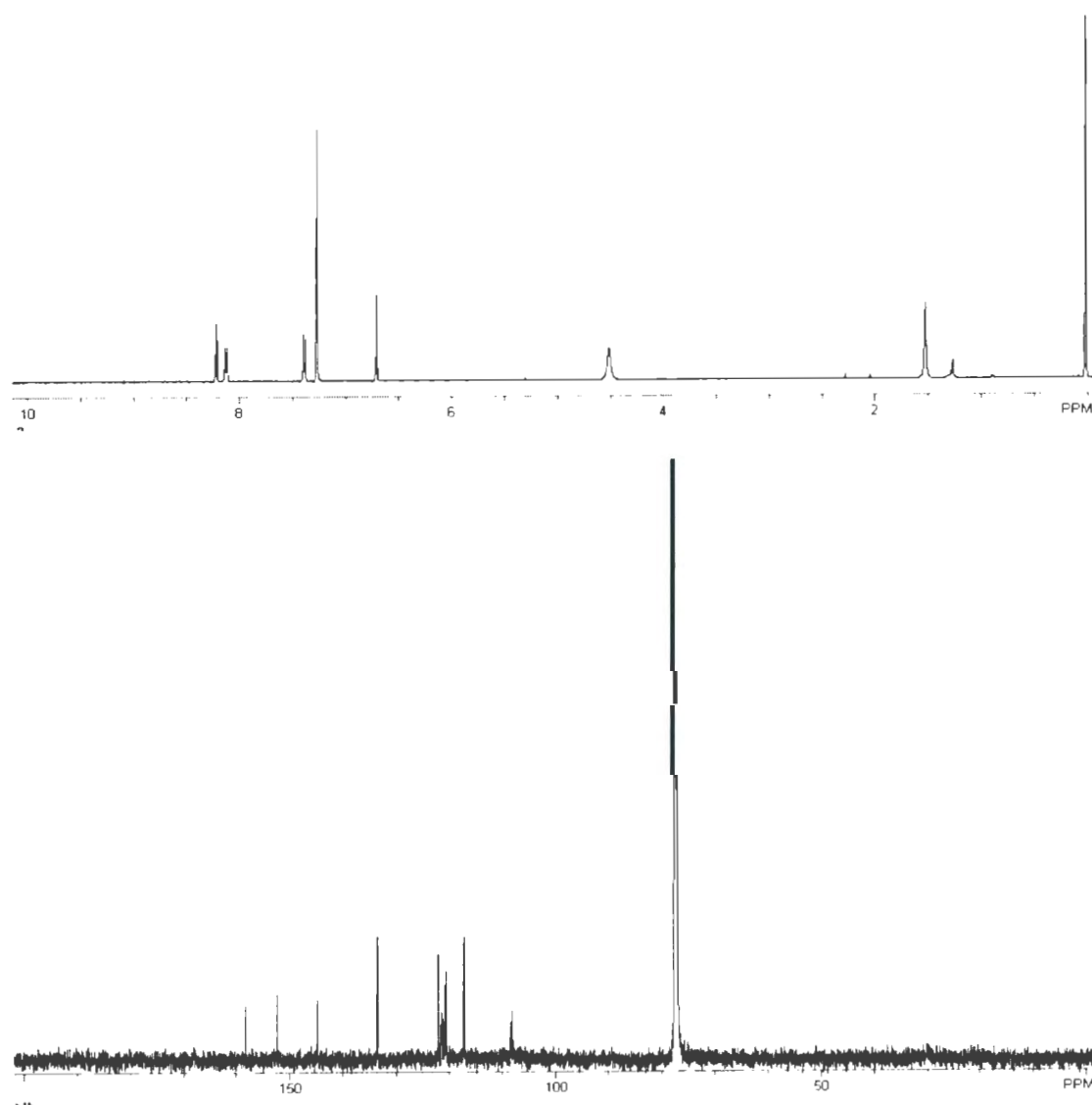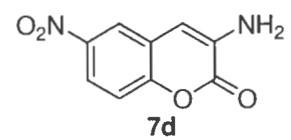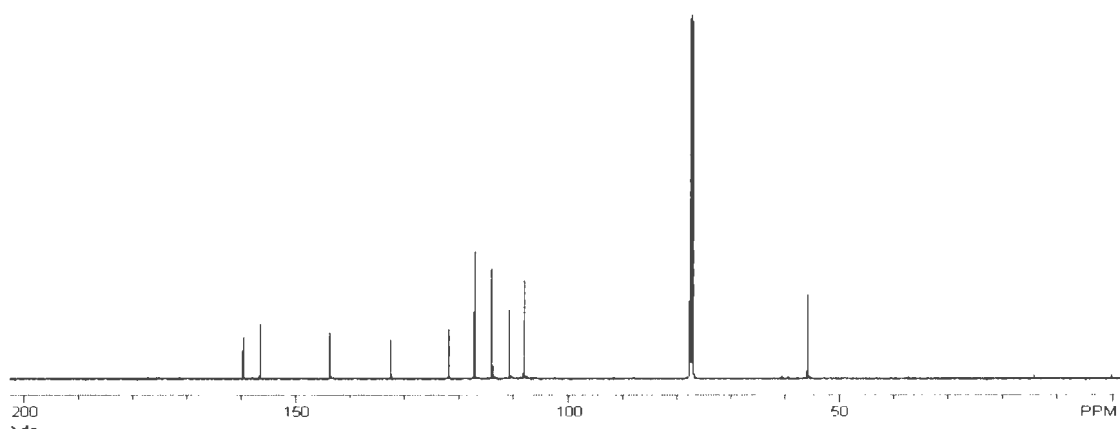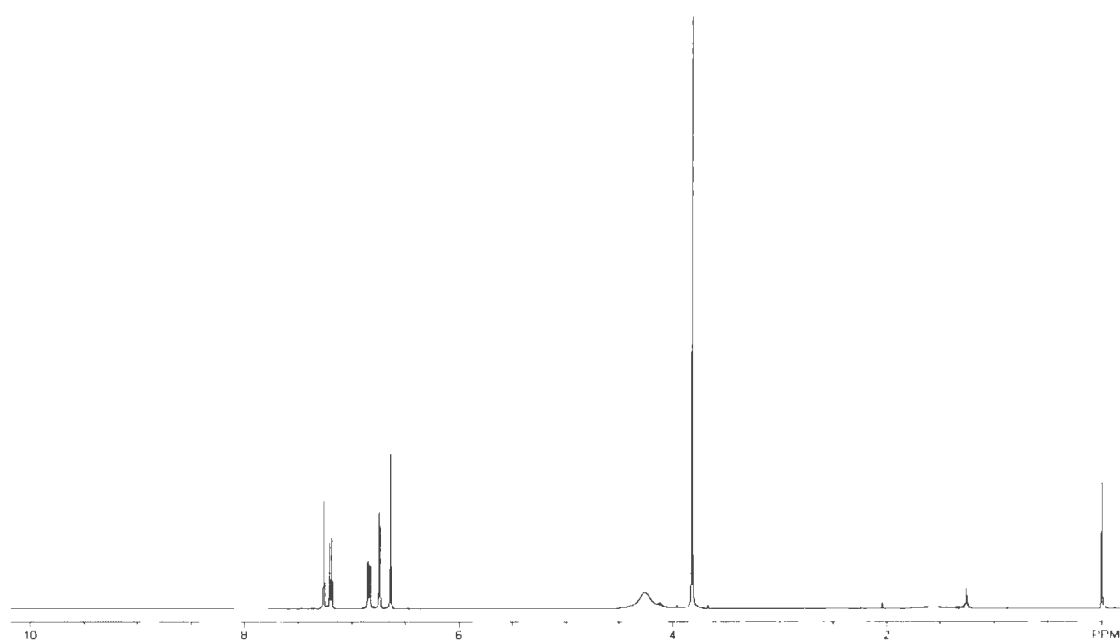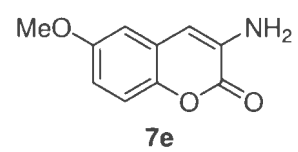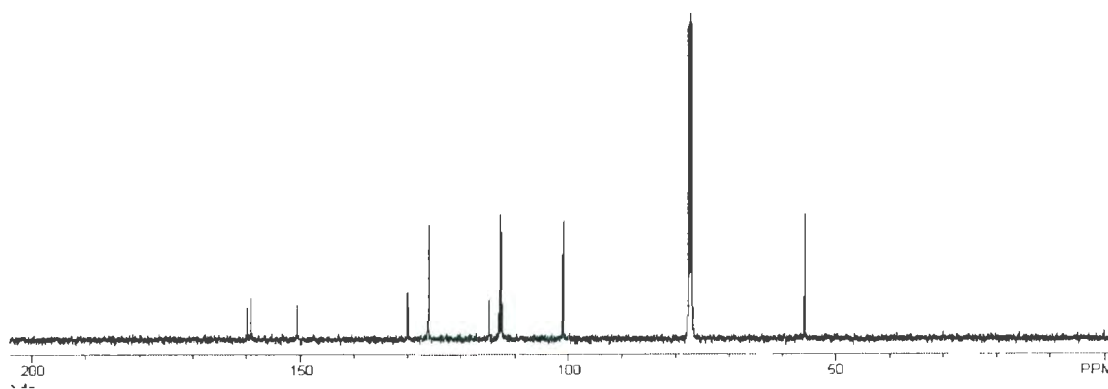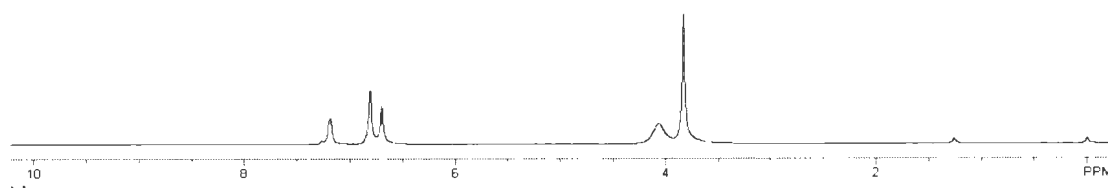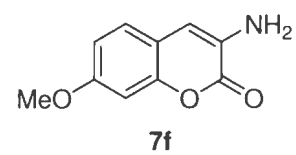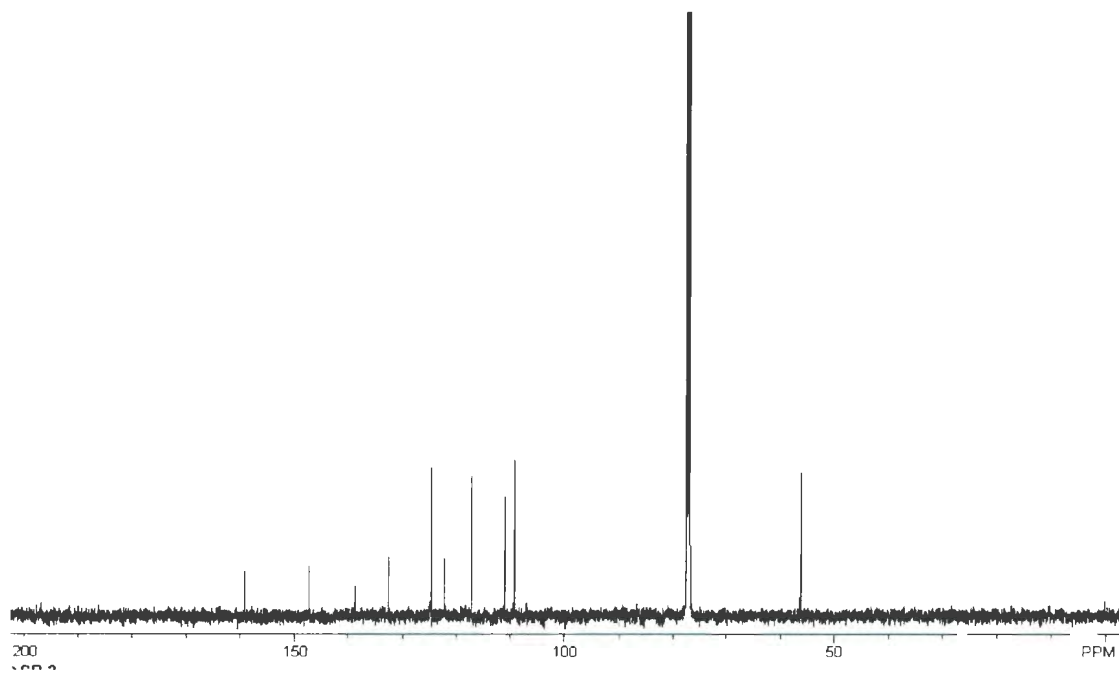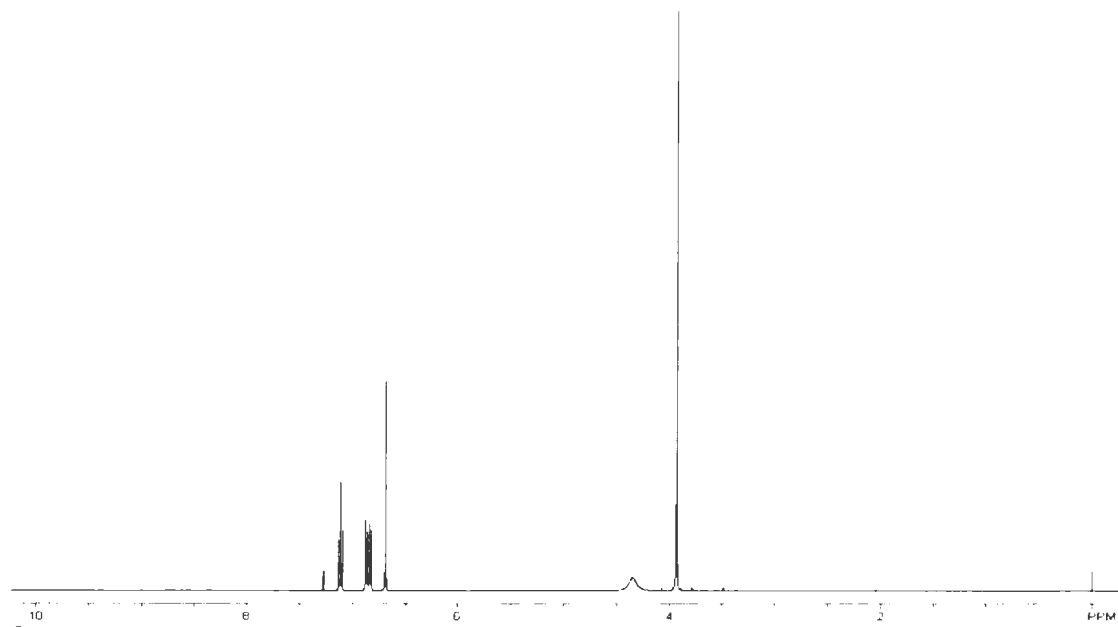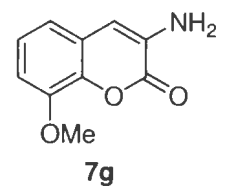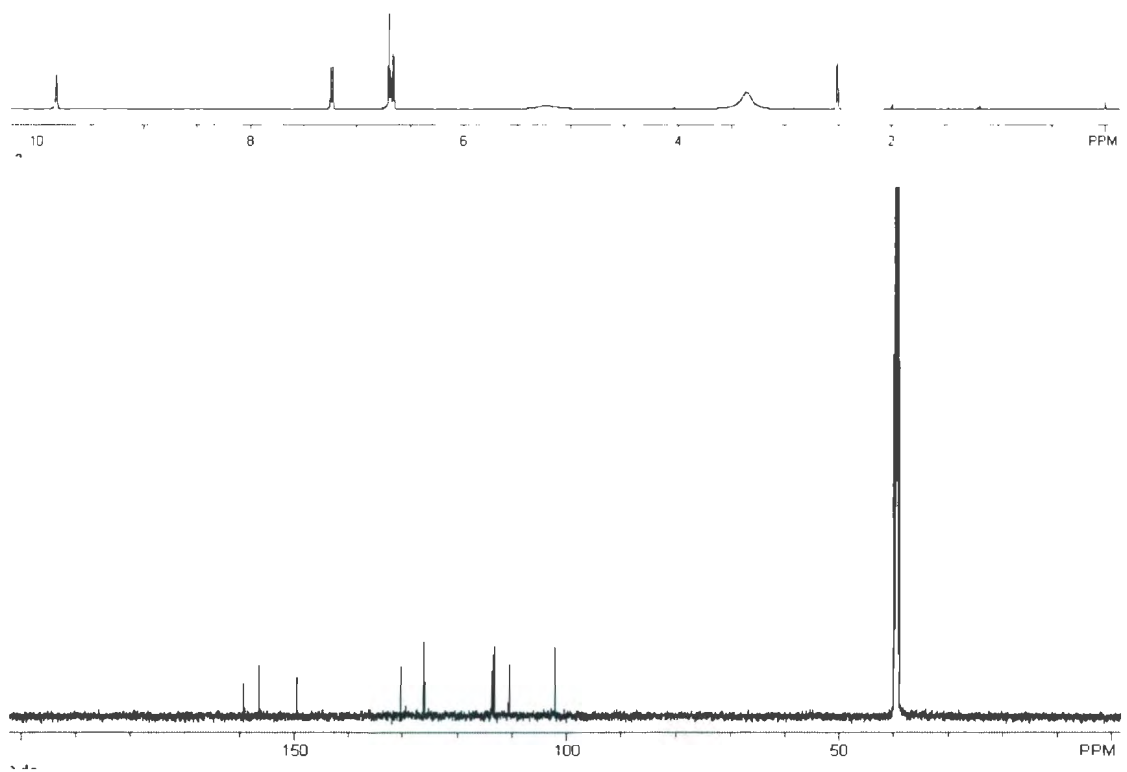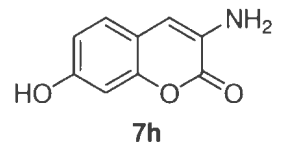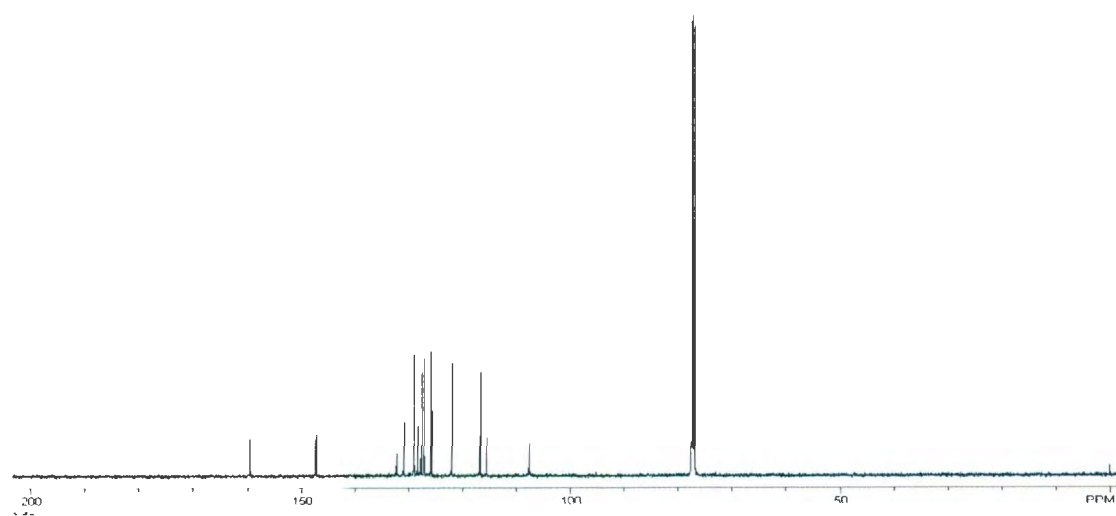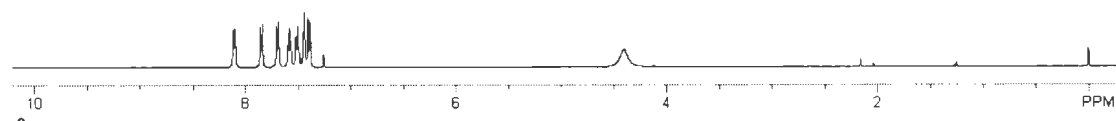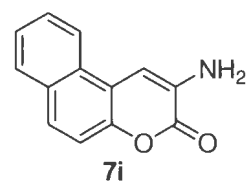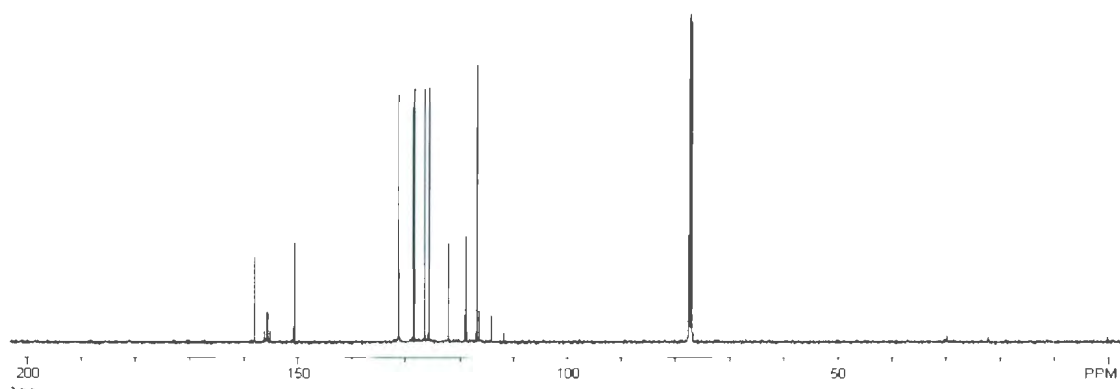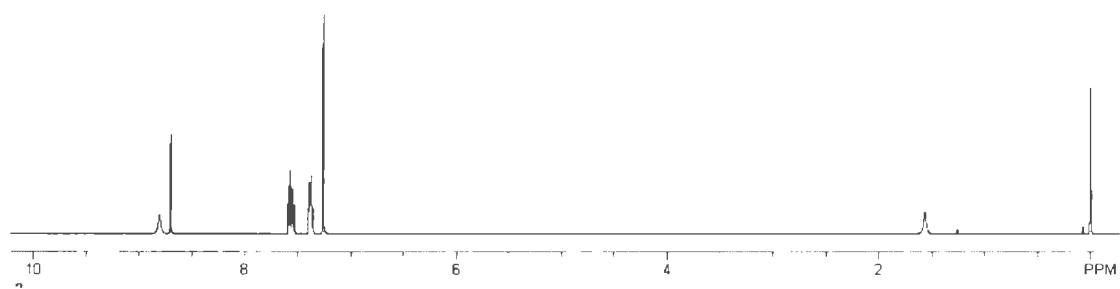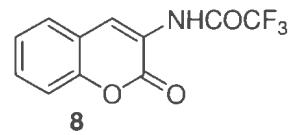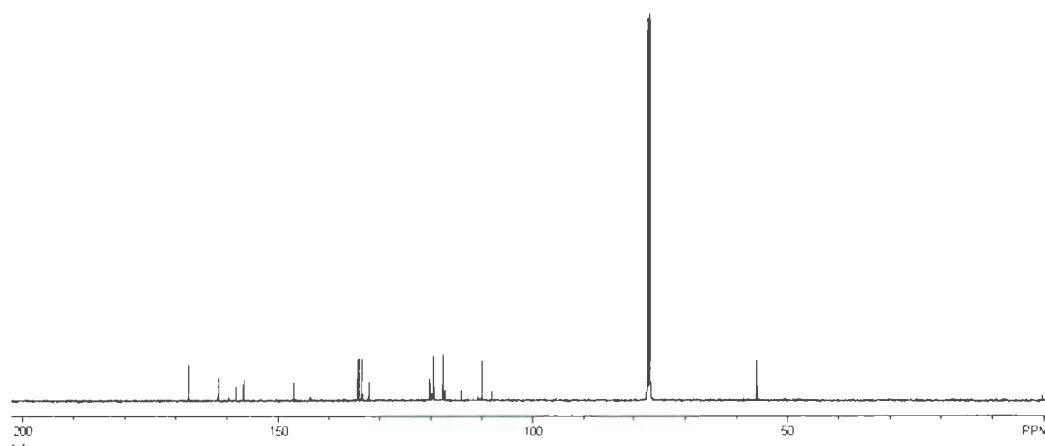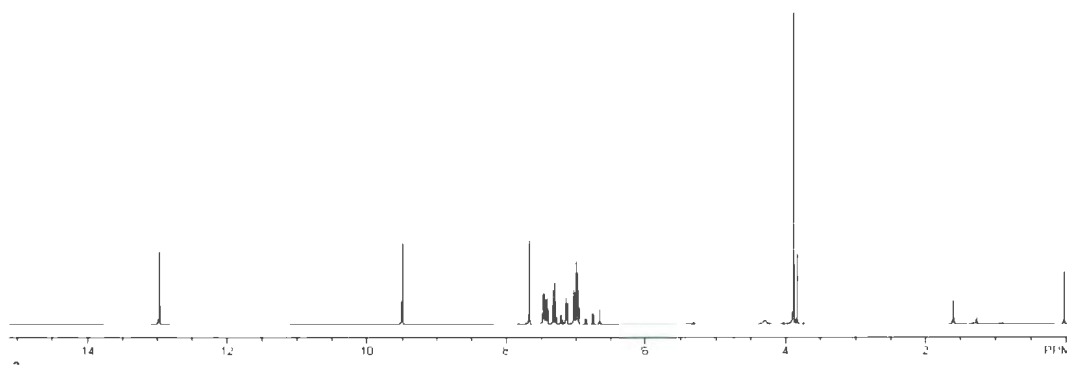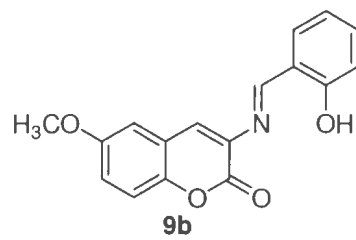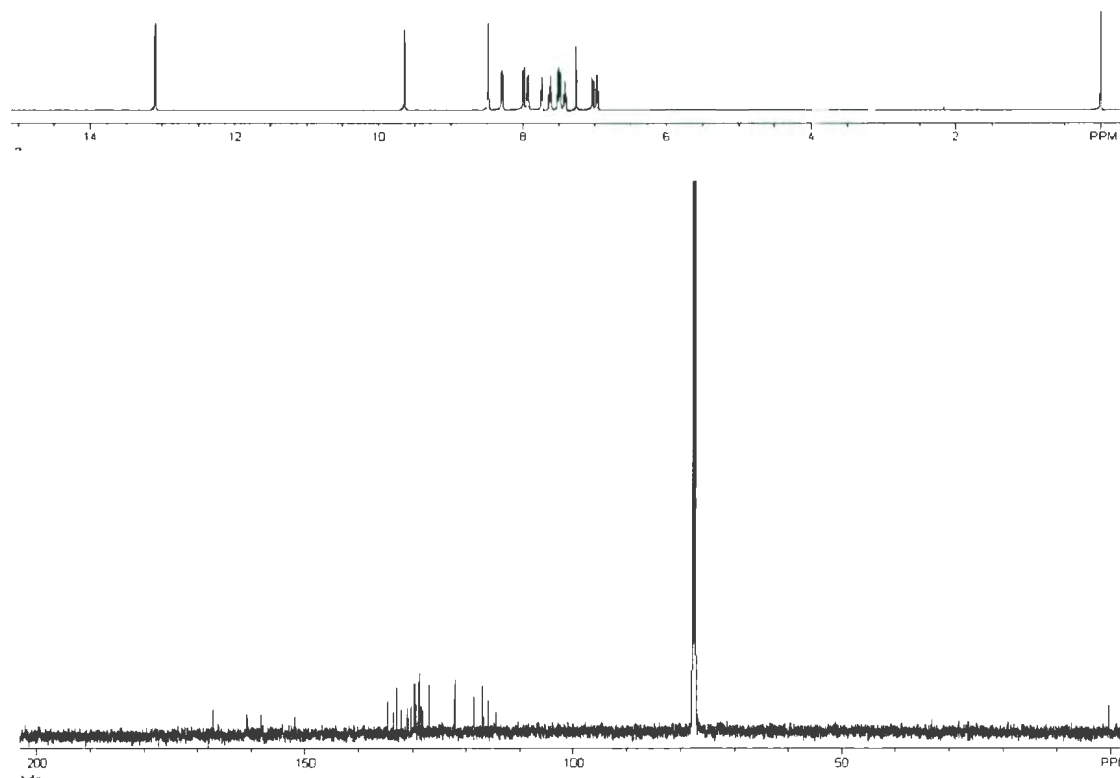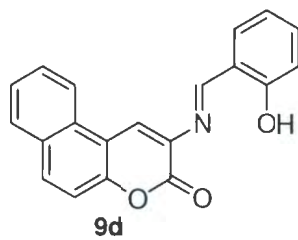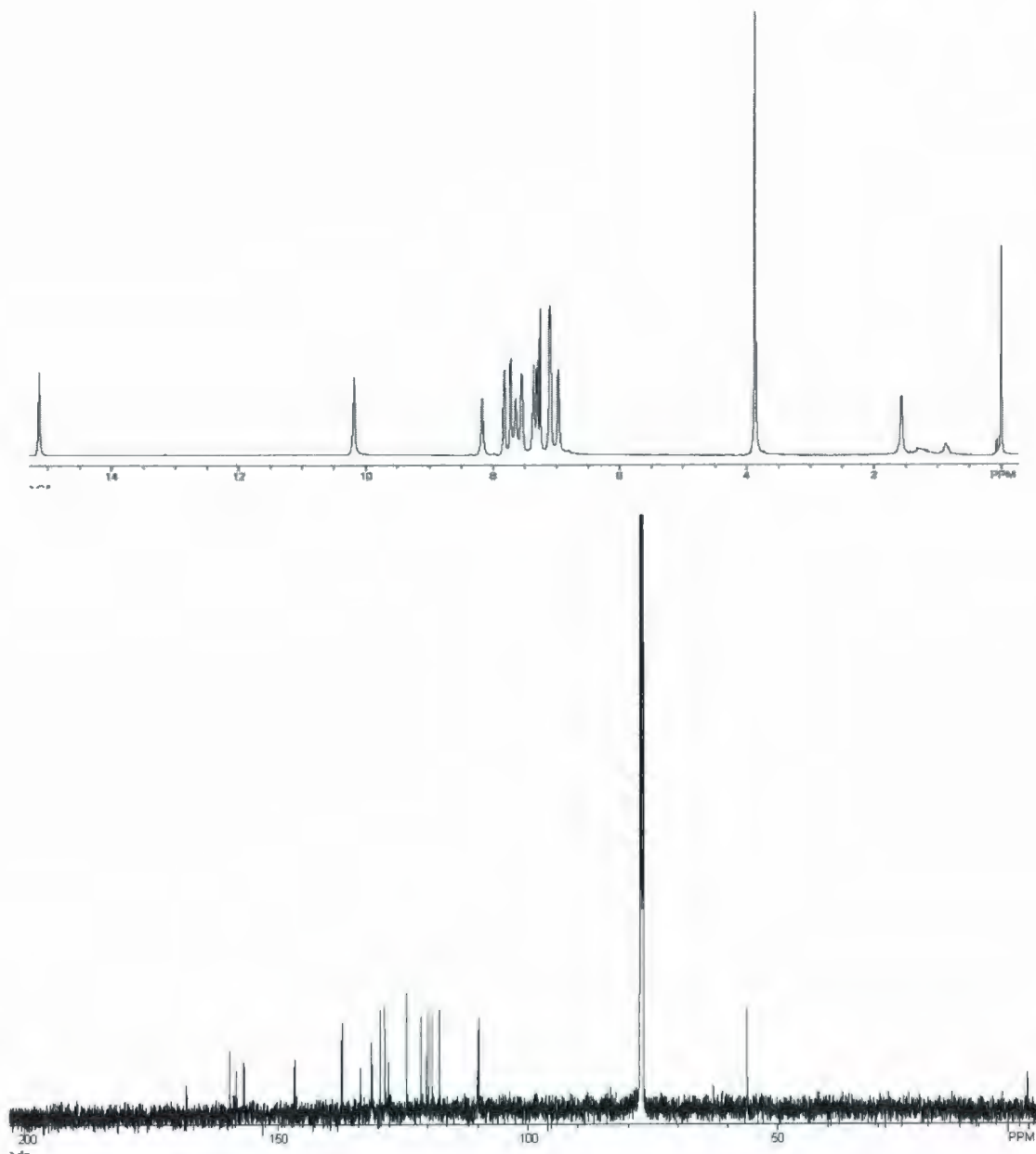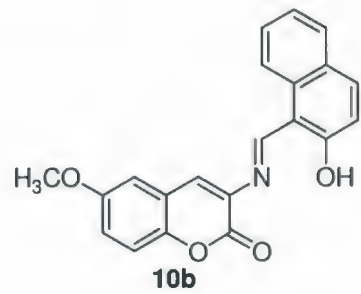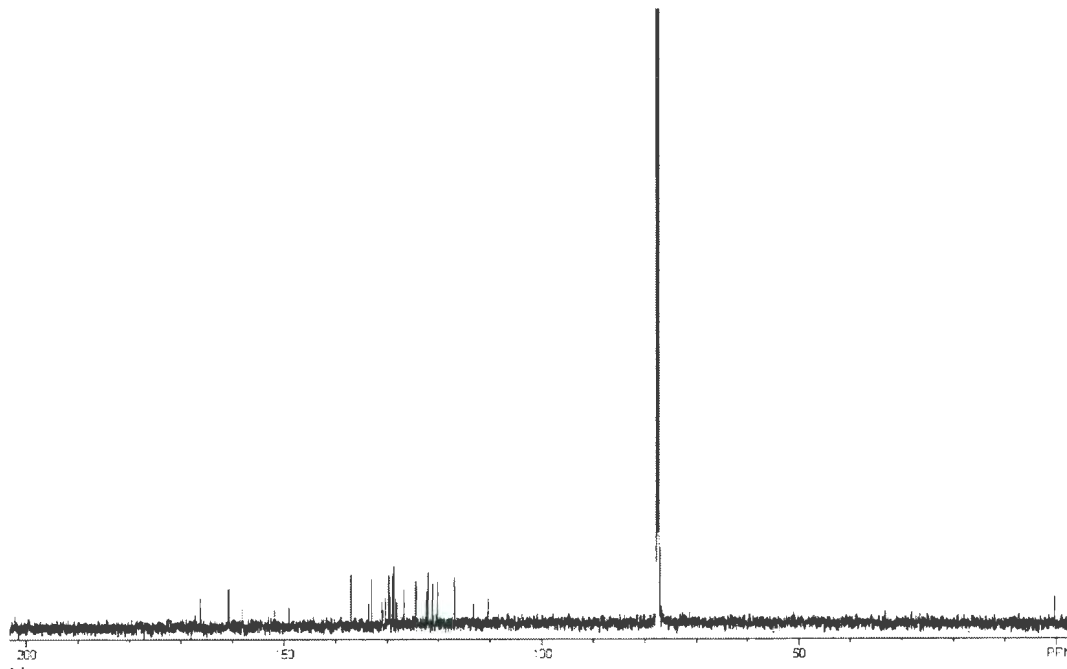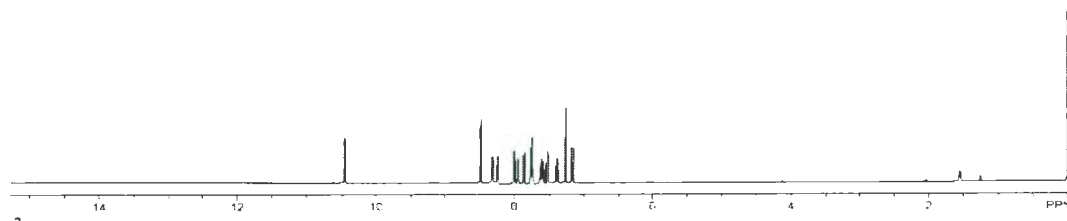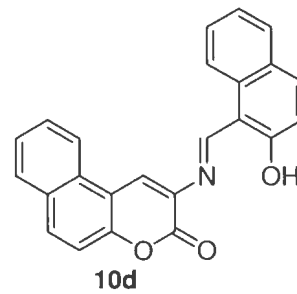
Chapter 2. Povarov Reactions Involving 3-Aminocoumarins: a Synthesis of 1,2,3,4-Tetrahydropyrido[2,3-*c*]coumarins and Pyrido[2,3-*c*]coumarins

2.1 Introduction

Multicomponent reactions (MCRs) continue to attract attention as they can result in a substantial increase in molecular complexity and provide opportunities for high levels of convergence in synthesis.[1] The use of MCRs has therefore been frequently adopted by the pharmaceutical industry for the development of combinatorial libraries and the identification of lead compounds.[2] MCRs have also been utilized in the total synthesis of natural products.[3]

The inherent reactivity of carbonyl compounds with amines is often exploited in the development of MCRs.[4] The one-pot version of the Povarov reaction is such an example. In its original form, however, the Povarov reaction was not an MCR. Povarov initially described the participation of aldimines derived from aniline and aromatic aldehydes in a formal [4+2] cycloaddition with electron rich alkenes (rendering it a formal inverse electron demand Diels-Alder reaction) in the presence of a Lewis acid catalyst and the subsequent tautomerization of the initial adduct to give 1,2,3,4-tetrahydroquinoline derivatives (Eq. 1, Scheme 2.1).[5] It was only much later that this

reaction was developed into a one-pot operation (MCR), in which the aldimine was generated *in situ*.[6] In fact, this development triggered an ongoing period of considerable interest in the Povarov reaction,[7] which followed nearly three decades of relative obscurity since Povarov's original report.[8]

SCHEME 2.1 The Povarov Reaction
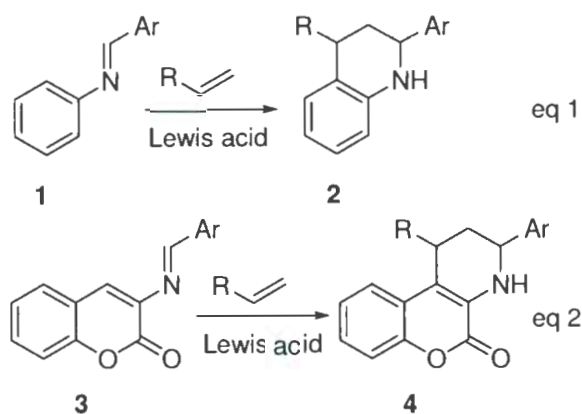
An important finding in the mid 1990s was that various lanthanide metal salts catalyze the one-pot Povarov reaction.[6] More recently, a variety of cost-effective and environment-friendly catalysts were reported by Perumal[7a-g] and others.[7i-n] In general, aliphatic aldehydes have been found to be poor participants in this type of chemistry. However, Batey and Menéndez have independently shown that aliphatic aldehydes or aldehyde equivalents can be employed under appropriate conditions (slow addition of the aldehyde or aldehyde equivalent to the aniline and dienophile in the presence of a mild Lewis acid).[9] This reaction has also been carried out in the absence of a Lewis acid catalyst by using fluorous solvents.[10] The Povarov reaction has also found applications in

total synthesis, such as in the synthesis of (±)-martinellic acid (**8**), (±)-martinelline (**9**), camptothecin (**14**) and luotonin A (**16**)[11] (Schemes 2.2, 2.3 and 2.4, respectively). Nevertheless, it has so far been limited almost exclusively to the synthesis of tetrahydroquinolines because, with very few exceptions,[12] only anilines have been used successfully as the amine component. The application of amines other than anilines, if successful, would provide a direct route to a variety of heterocycles, which are uncommon or otherwise not easily accessible.

SCHEME 2.2 Total Synthesis of (±)-Martinellic Acid (**8**) and (±)-Martinelline (**9**)

8 R = H   (±)-martinellic acid

9 R = (±)-martinelline
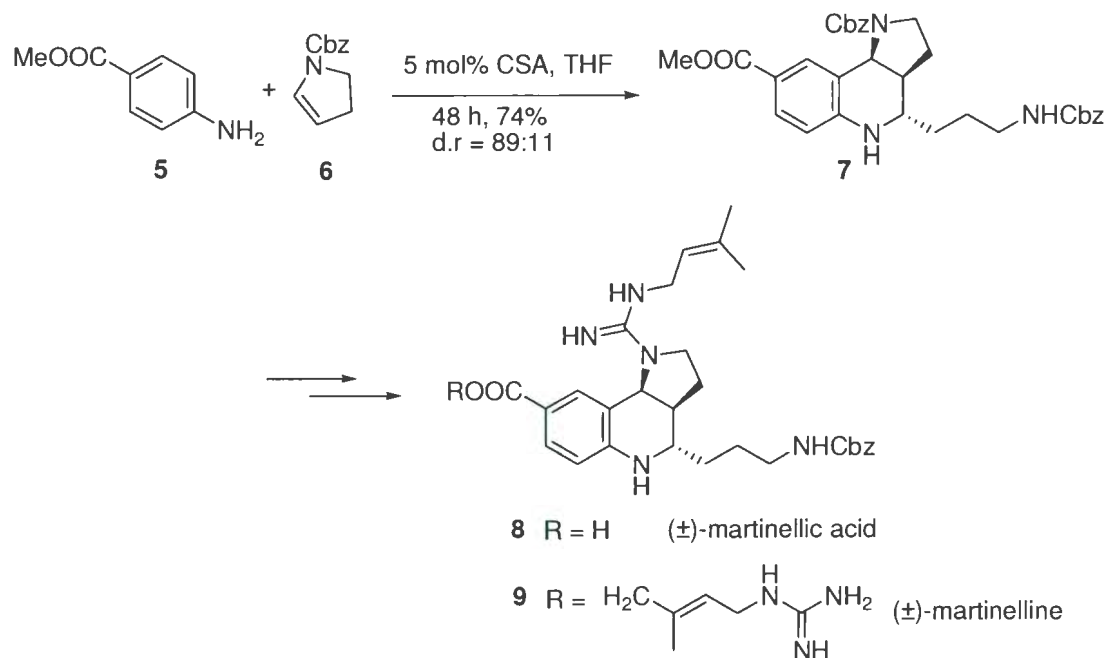
SCHEME 2.3 Formal Total Synthesis of Camptothecin (14)
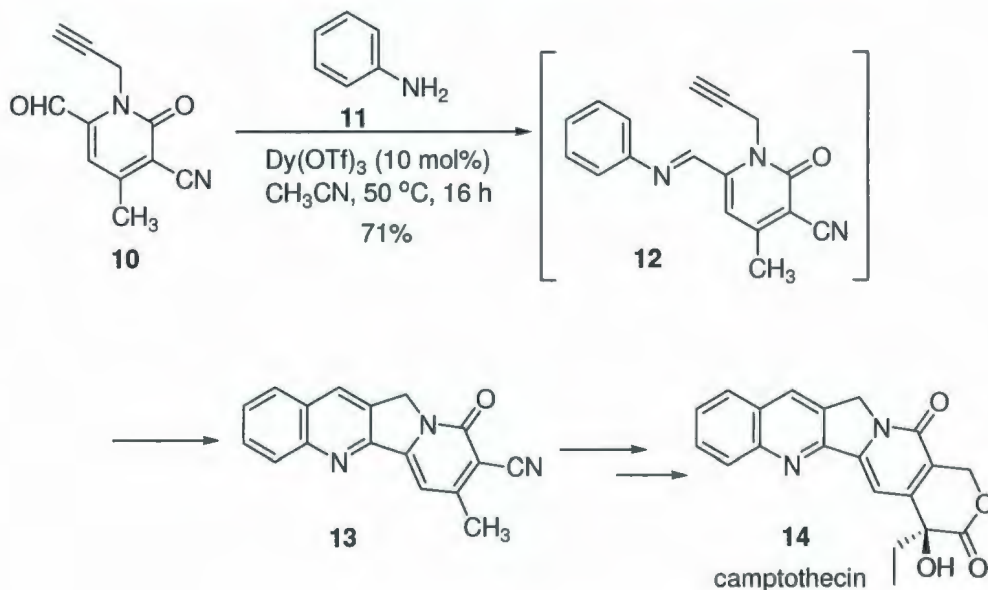
SCHEME 2.4 Synthesis of Luotonin A (16)
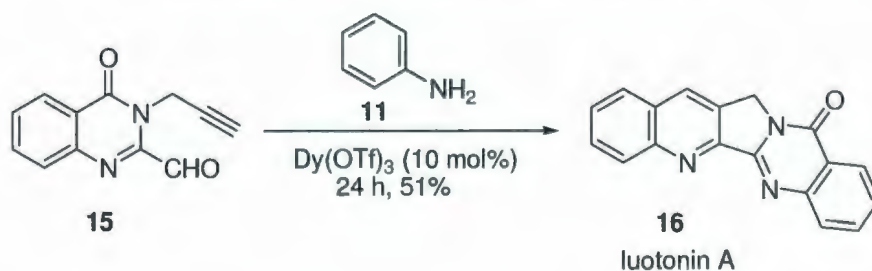
During the course of our efforts aimed at the development of new families of electron deficient dienes for application in the inverse electron demand Diels-Alder (IEDDA) reaction,[13] coumarin-fused, electron deficient 2-azadienes were identified as reasonable candidates for reaction with electron rich alkenes. In fact, the IEDDA reaction of this class of dienes, which should be accessible from the condensation of 3-

aminocoumarin with an aldehyde, coincides with the original form of the Povarov reaction. 3-Aminocoumarin has been known for close to a century, but there are very few reports of imines derived from this system.[14] There are no previous reports of such imines being used as dienes in the IEDDA (or Povarov) reaction. The 2-pyrone ring of the coumarin system is partially aromatic.[15] As such, 3-aminocoumarins behave like enamines in some cases (*e.g.* hydrolysis under acidic aqueous conditions)[16] and like anilines in others (*e.g.* Fischer indole synthesis).[17] We thus envisioned that 3-aminocoumarin (**17**) would readily form an aldimine upon reaction with an aldehyde and then take part in a Povarov reaction in the presence of an electron rich alkene and a suitable Lewis acid catalyst. The partial aromatic character of the pyrone unit would also be expected to favor the tautomerization of the initial cycloadduct (Scheme 2.5).

SCHEME 2.5 The Povarov Reaction Involving 3-Aminocoumarin
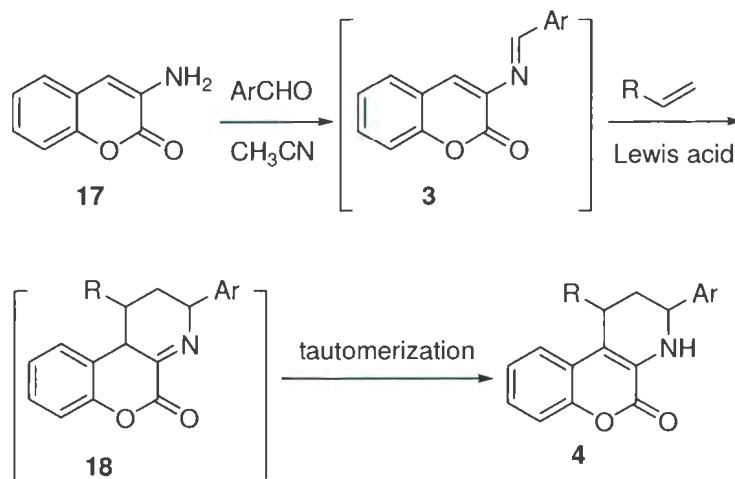
2.2 Results and Discussion

Preliminary work on this concept was performed earlier in the Bodwell group.[18] A coumarin-fused 2-azadiene **20**, which was prepared by the condensation of 3-aminocoumarin (**17**)[19] and 4-nitrobenzaldehyde (**19**) using modified Bishnoi conditions[20] was shown to participate in the Povarov reaction with electron rich alkenes such as 3,4-dihydro-2H-pyran (DHP) in the presence of Yb(OTf)$_3$ as a Lewis acid (Scheme 2.6). The yields were generally good and the diastereoselectivity of the reaction ranged from >95:5 (for '*endo* adduct') to 8:92 (for '*exo* adduct').

SCHEME 2.6 Povarov Reaction between a Coumarin-fused 2-Azadiene **20** and DHP

(**21**)
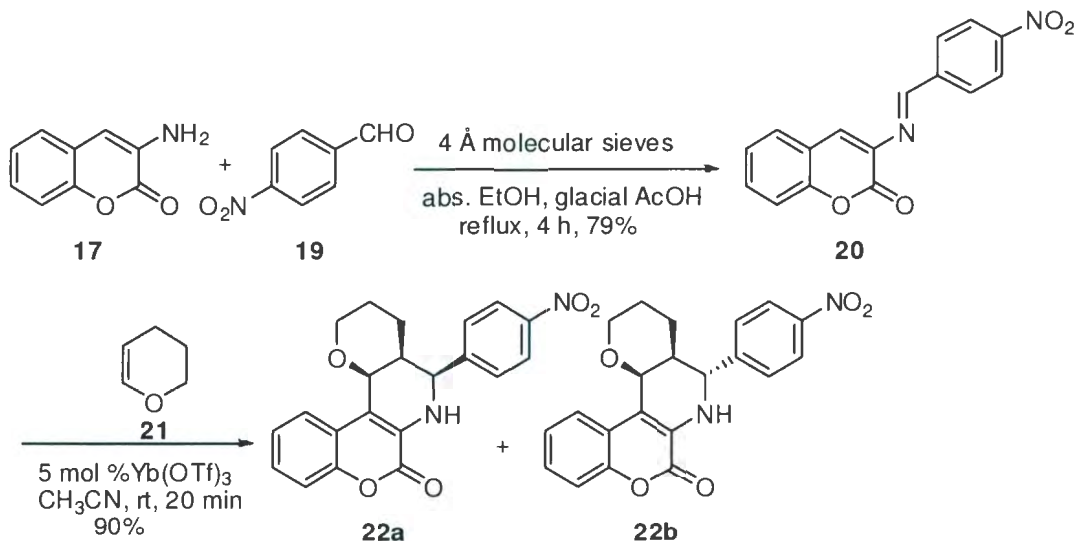
Having this precedent, the possibility of developing this reaction into a one-pot operation, in which the diene would be formed *in situ* from 3-aminocoumarin and an

aldehyde, was investigated. Indeed, the reaction of 3-aminocoumarin (**17**), 4-nitrobenzaldehyde (**19**) and DHP (**21**) in the presence of 5 mol% Yb(OTf)$_3$ afforded Povarov adducts **22a,b** in a similar ratio (39:61) to the reaction of diene **20** with DHP (**21**) (36:64), but with a lower yield (40% *cf.* 90%) (Scheme 2.7).

Other products were observed by tlc analysis of this one-pot reaction, but none of these could be obtained in pure form. The possibility that water generated during the formation of 2-azadiene **20**, might have adversely affected the yield was ruled out when a similar yield (42%) of Povarov adducts **22a,b** was obtained when the same reaction was performed in the presence of anhydrous MgSO$_4$. This suggested that some other factor(s) is (are) affecting the yield of this one-pot Povarov reaction and hence an optimization study for this reaction was undertaken.

SCHEME 2.7 One-pot Povarov Reaction
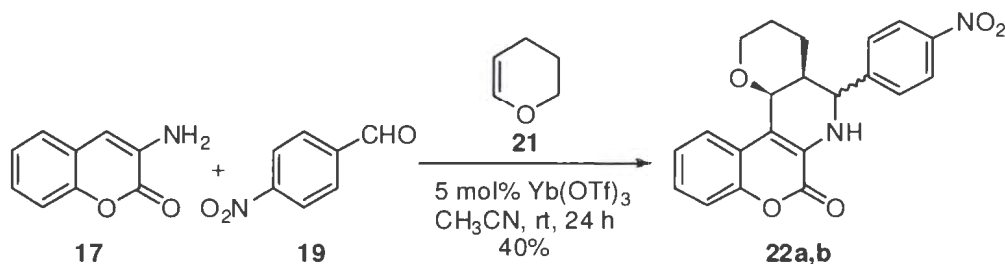
2.2.1 Optimization Study for the One-pot Povarov Reaction

The study of the effect of various Lewis acids and solvents on the yield and diastereoselectivity of the one-pot reaction was the starting point for this study (Table 2.1). To this end, a set of reactants was required, the products of which would be easily

separable from the side products so that the isolated yields and diastereomeric ratios could be determined easily. After some experimentation, it was found that the reaction between 3-aminocoumarin (17), 2-naphthaldehyde (23) and DHP (21) met this criterion. Under the previously employed conditions (Scheme 2.7), two diastereomeric products, 24a and 24b, were isolated in a 21:79 ratio in 56% combined yield (Scheme 2.8).[21] The two diastereomers were formally the products of *endo* and *exo* addition in an IEDDA reaction followed by tautomerization of the initial cycloadduct. The relative stereochemistry was determined using standard 1D and 2D NMR techniques. Although the retention of the relative stereochemistry of the dienophile in both adducts is entirely consistent with a concerted mechanism, a stepwise mechanism cannot be ruled out.[22] If a stepwise mechanism is operating, the ring closure must occur in a highly diastereoselective fashion.

SCHEME 2.8 One-pot Povarov Reaction between 3-Aminocoumarin (17), 2-Naphthaldehyde (23) and DHP (21)

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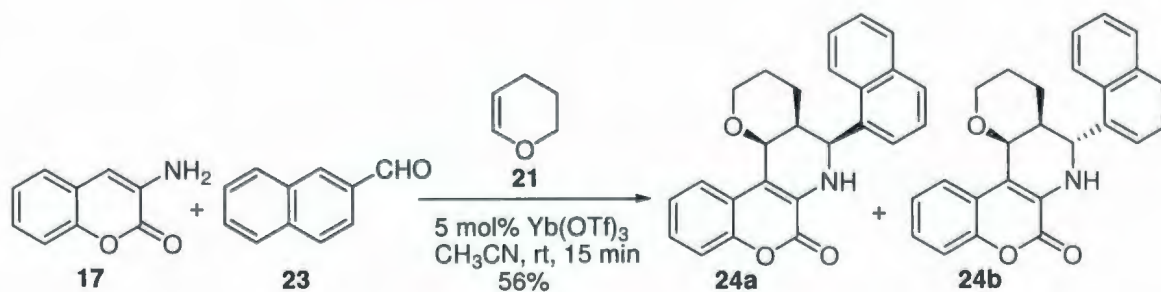
Kobayashi and co-workers have shown that various lanthanide metal salts catalyze the Povarov reaction.[6] Therefore, the performance of $Dy(OTf)_3$ (Entry 2, Table 2.1) and $CeCl_3 \cdot 7H_2O$ (Entry 3, Table 2.1) were also evaluated in the one-pot reaction. Neither of these catalysts fared better than the original choice, $Yb(OTf)_3$. Lower yields (28% and 25%, respectively) and poor diastereoselectivity (43:57 and 38:62, respectively) were obtained. The yields increased with an increase in the oxophilic character (according to the oxophilicity scale developed by Imamoto and coworkers)[24] of lanthanide salts. This finding was in agreement with previous reports on the activity of various lanthanide salts as Lewis acids.[25] Following the reports of the use of cheap and environmentally benign catalysts for the parent Povarov reaction, the effect of catalysts such as molecular iodine (I_2)[7n,o] (Entry 7, Table 2.1), potassium hydrogen sulfate $(KHSO_4)$[7d] (Entry 6, Table 2.1) and silica gel[26] was also studied. Silica gel did not catalyze the reaction at room temperature or reflux (Entries 4 and 5, Table 2.1). Conversely, I_2 and $KHSO_4$ afforded yields and diastereoselectivities comparable to those obtained using $Yb(OTf)_3$.

Using $Yb(OTf)_3$ as the Lewis acid, the effect of solvent was then investigated. A low yield (10%) and no diastereoselectivity (50:50) were observed for $CHCl_3$ (Entry 11, Table 2.1). Although very good diastereoselectivity ($\approx$ 1:9) was achieved in polar protic solvents (methanol and methanol/water), the reaction was very slow. Traces of one of the starting materials, 3-aminocoumarin (17), were present in the reaction (by tlc analysis) even after refluxing for 24 and 48 h, respectively (Entries 12 and 13, Table 2.1). The addition of methanol and/or water to the C=N bond of the 2-azadiene may be responsible

for the slow reaction of the azadiene. The use of a somewhat less polar solvent, THF (Entry 14, Table 2.1), or THF with water as a co-solvent (Entry 15, Table 2.1) did not improve the yields (41% and 16%, respectively) as compared to acetonitrile. In a nonpolar solvent, toluene, a low yield (28%) and a low diastereomeric ratio (38:62) were obtained (Entry 16, Table 2.1), whereas in a polar aprotic solvent, DMF, the reaction did not proceed appreciably after 2 hours at room temperature. Except for $CHCl_3$ and DMF, the yields increased with an increase in the dielectric constant of the solvent (when the reactions were run without a co-solvent). Thus, acetonitrile proved to be the best among the solvents screened.

Based on the results of the solvent study, some comments can be made on the mechanism. For Povarov reactions of aniline-derived 2-azadienes, a product arising from the nucleophilic addition of methanol to an intermediate oxonium ion has been reported, which suggests a stepwise mechanism.[6b,7x] No such product was isolated from the above reactions (Entries 12 and 13, Table 2.1). Moreover, the yield of the Povarov adducts was not significantly affected. These observations suggest that, in contrast to the Povarov reactions of aniline-derived 2-azadienes, the Povarov reactions of 2-azadiene **9** most likely proceed through a concerted, yet asynchronous, mechanism. The difference in mechanism may be a consequence of the considerably weaker aromatic character of the 2-pyrone unit in coumarin-derived azadienes compared to that in the benzene ring of aniline-derived azadienes. In other words, a concerted reaction of an aniline-derived azadiene would be disfavoured more than the corresponding reaction of a coumarin-derived azadiene because of a greater loss of aromatic stabilization energy in going from

the ground state to the transition state.

As anticipated, the diastereomeric ratio could be improved by lowering the temperature, but this occurred at the expense of the yield (Entries 8-10, Table 2.1). Yields of 44%, 19% and 7% were obtained when the reactions were performed at 0 °C, –20 °C and –30 °C, respectively. At –30 °C, the reaction was quite sluggish and 54% of the starting 3-aminocoumarin (**17**) was recovered after running the reaction for 4 h.

TABLE 2.1 Effect of the Catalyst and Solvent on the Povarov Reaction of **17** with **23** and **21**
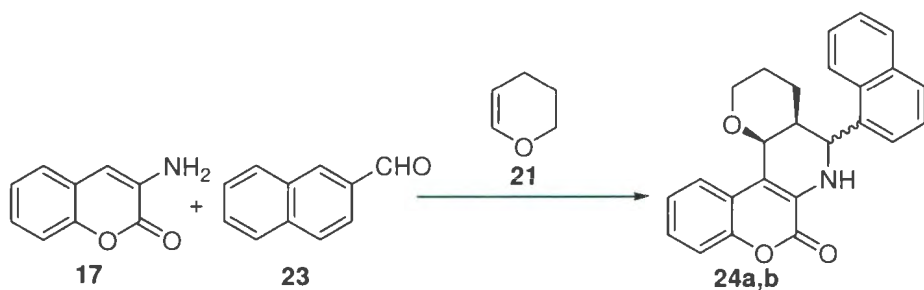
Entry	Catalyst	Solvent	Temperature	*endo/exo* ratio[a]	Combined Yield (%)[b]
1	5 mol% Yb(OTf)$_3$	CH$_3$CN	rt	21:79	56
2	5 mol% Dy(OTf)$_3$	CH$_3$CN	rt	43:57	28
3	10 mol% CeCl$_3$·7H$_2$O	CH$_3$CN	rt	38:62	25
4	silica gel	CH$_3$CN	rt	-	no reaction
5	silica gel	CH$_3$CN	reflux	-	no reaction

6	40 mol% $KHSO_4$	CH_3CN	rt	18:82	52
7	30 mol% I_2	CH_3CN	rt	28:72	53
8	5 mol% $Yb(OTf)_3$	CH_3CN	0 °C	15:85	44
9	5 mol% $Yb(OTf)_3$	CH_3CN	–20 °C	9:91	19
10	5 mol% $Yb(OTf)_3$	CH_3CN	–30 °C	≤5:95	7
11	5 mol% $Yb(OTf)_3$	$CHCl_3$	rt	50:50	10
12	5 mol% $Yb(OTf)_3$	MeOH	reflux	12:88	45
13	5 mol% $Yb(OTf)_3$	$MeOH/H_2O$	reflux	8:92	46
14	5 mol% $Yb(OTf)_3$	THF	rt	24:76	41
15	5 mol% $Yb(OTf)_3$	THF/H_2O	rt	53:47	16
16	5 mol% $Yb(OTf)_3$	toluene	rt	38:62	28
17	5 mol% $Yb(OTf)_3$	DMF	rt	-	no reaction

[a] Diastereomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. [b] Isolated yields.

2.2.2 Scope of the One-pot Povarov Reaction

Based on the optimization studies, the scope of the one-pot reaction was investigated by varying the three components. To begin with, the aldehyde component, which provides C-1 of the azadiene and the substituent attached to it, was varied while the 3-aminocoumarin (**17**) and the dienophile (DHP) were kept constant (Table 2.2). The conditions used for the synthesis of **24a,b** (Entry 1, Table 2.1) were employed. Application of a heterocyclic aldehyde, 3-formylcoumarin (**25**),[27] in the three-component reaction with 3-aminocoumarin (**17**) and DHP (**21**) in presence of $Yb(OTf)_3$ in

acetonitrile (Entry 2, Table 2.2) proceeded smoothly at room temperature to afford tetrahydropyrido[2,3-*c*]coumarins **26a,b** in a ratio of 36:64 in favor of the *exo* diastereomer and 71% combined yield. The more electron deficient nature of the aldehyde **25** (compared to aldehyde **23**) appeared to have a positive effect on the yield of the Povarov adducts.

When 3-aminocoumarin (**17**) was reacted with methyl 4-formylbenzoate (**27**) and DHP (**21**), Povarov adduct **28b** was obtained with very high selectivity (<5:95) in 54% yield (Entry 3, Table 2.2). By the same token, very high selectivity (≤5:95) in favor of the *exo* diastereomer was obtained when 3-aminocoumarin (**17**) was reacted with 4-acetoxybenzaldehyde (**29**) and DHP (**12**) to afford Povarov adduct **30b**. However, the yield was only 26% (Entry 4, Table 2.2). The mild electron donating ability of the acetoxy group in 4-acetoxybenzaldehyde, which would be expected to attenuate the electron deficient nature of the *in situ* formed 2-azadiene, might be responsible for the low yield.

For the highest-yielding reaction in the above set of reactions (Entry 2, Table 2.2), changing the dienophile from DHP (**21**) to 2,3-dihydrofuran (DHF) (**31**) resulted in the formation of Povarov adducts **32a,b** in 58% yield. The diastereoselectivity (42:58) was close to that observed when DHP was used (*cf.* Entries 2 and 5, Table 2.2). Employment of ketone-containing heterocyclic aldehyde **33**[28] afforded Povarov adducts **34a,b** in relatively good yield (59%, Entry 6, Table 2.2). Isolation of the *endo* diastereomer was very difficult in this reaction. Only the *exo* diastereomer **34b** could be isolated in pure form. This experiment also demonstrated that the three-component reaction could be

performed in the presence of a potentially competitive ketone functionality. When 4-acetoxybenzaldehyde (**29**) was employed, a low yield (33%) and poor diastereoselectivity (46:54) were obtained (Entry 7, Table 2.2). The reaction had to be heated at reflux for 2.5 days to achieve complete consumption of the starting 3-aminocoumarin (**17**).

The 3-aminocoumarin was then varied while the dienophile (DHF) and the aldehyde (methyl 4-formylbenzoate) were kept constant. In general, all of these reactions afforded low yields and diastereoselectivities (Entries 8-11, Table 2.2). In most cases, the 3-aminocoumarins bore an electron donating substituent on the carbocyclic ring, which would be expected to deactivate the diene. However, surprisingly, the reaction involving 3-amino-6-nitrocoumarin (Entry 11, Table 2.2) afforded the lowest yield of all (28%). In this case, the formation of the 2-azadiene may have been retarded. The reaction of 3-amino-8-methoxycoumarin and 4-acetoxybenzaldehyde (**29**) with DHF under the same reaction conditions (Entry 12, Table 2.2) afforded a 60% yield of the Povarov adducts **40a,b** in a 38:62 ratio.
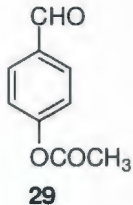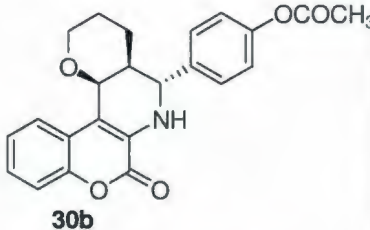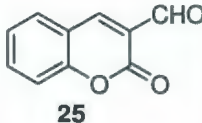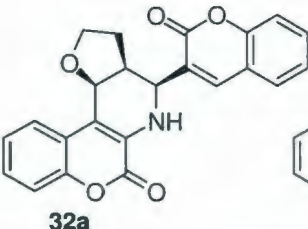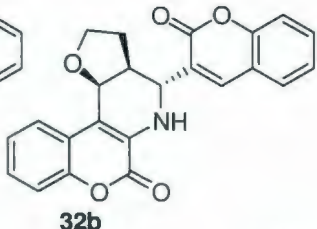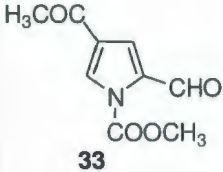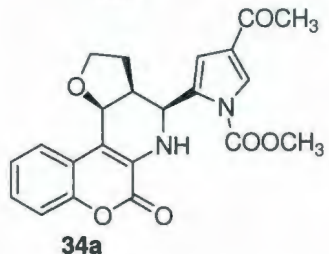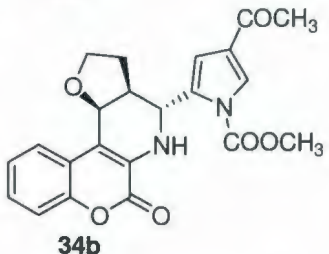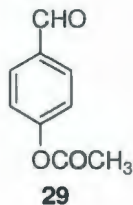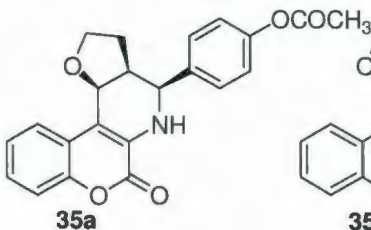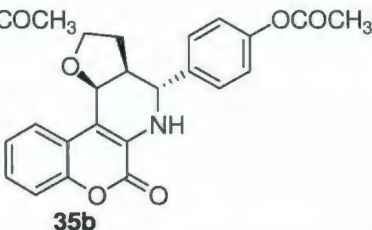
Phenyl vinyl sulfide, when reacted with 3-aminocoumarin (**17**) and 4-nitrobenzaldehyde (**19**) afforded a mixture (59:41) of the diastereomeric Povarov adducts **42a,b** in 38% yield (Entry 13, Table 2.2). It is interesting to note that the formation of the *endo* diastereomer is preferred in this reaction. Also, the yield of this reaction was low (38%) compared to the Povarov reaction performed on azadiene **20** with phenyl vinyl sulfide as a dienophile (81%). In general, the reaction times were usually short and yields were satisfactory for the above set of aldehyde and dienophile components with
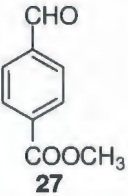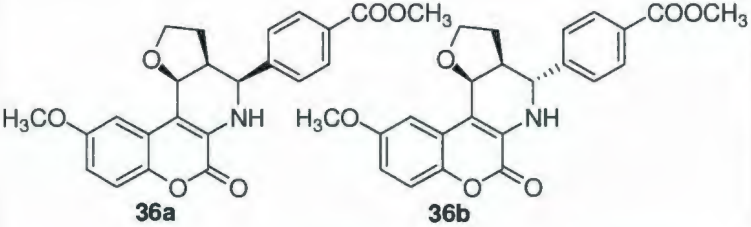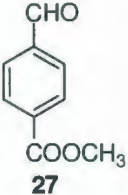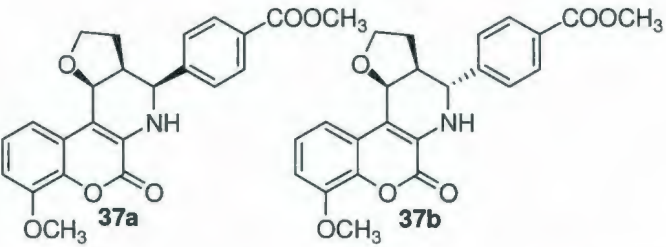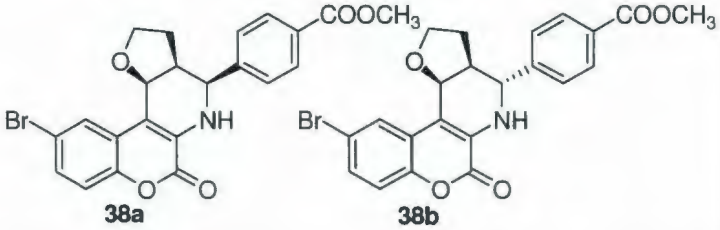
TABLE 2.2 Three-Component Synthesis of Pyrido[2,3-c]coumarins
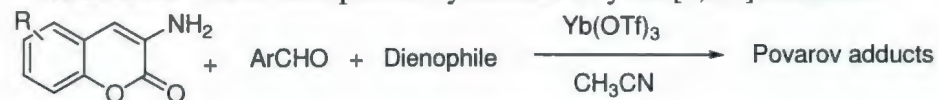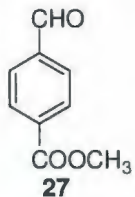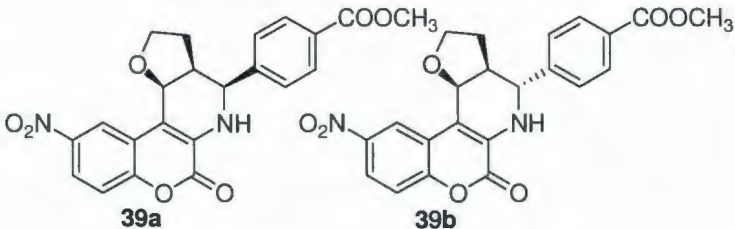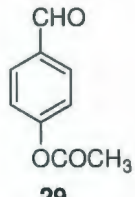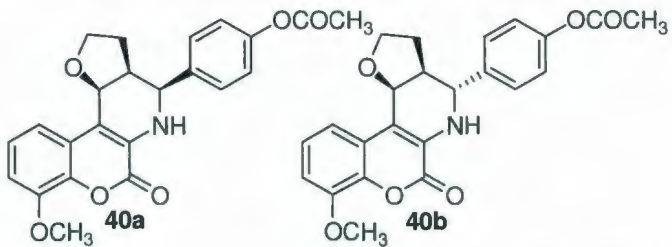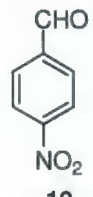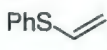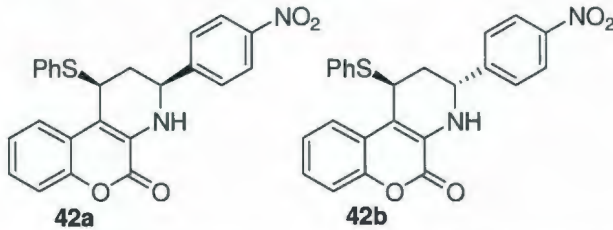
Entry	R	Aldehyde	Dienophile	Products	*endo/exo* ratio[a]	Yield (%)[b,c]
1	H	23	21	24a 24b	21:79	56 (89)
2	H	25	21	26a 26b	36:64	71
3	H	27	21	28b	<5:95	54

Entry	R	Aldehyde	Dienophile	Products	*endo/exo* ratio[a]	Yield (%)[b,c]
4	H	**29**	**21**	**30b**	<5:95	26
5	H	**25**	**31**	**32a**, **32b**	42:58	58
6	H	**33**	**31**	**34a**, **34b**	44:56	59
7	H	**29**	**31**	**35a**, **35b**	46:54	33

92

Entry	R	Aldehyde	Dienophile	Products	*endo/exo* ratio[a]	Yield (%)[b,c]
8	6-OCH$_3$	**27** (CHO, COOCH$_3$)	**31**	**36a** / **36b**	39:61	34
9	8-OCH$_3$	**27** (CHO, COOCH$_3$)	**31**	**37a** / **37b**	36:64	34 (54)
10	6-Br	**27** (CHO, COOCH$_3$)	**31**	**38a** / **38b**	44:56	30 (19)

93

Entry	R	Aldehyde	Dienophile	Products	*endo/exo* ratio[a]	Yield (%)[b,c]
11	6-NO$_2$	CHO ... COOCH$_3$ **27**	**31**	**39a** **39b**	42:58	28 (19)
12	8-OCH$_3$	CHO ... OCOCH$_3$ **29**	**31**	**40a** OCH$_3$ **40b** OCH$_3$	38:62	60
13	H	CHO ... NO$_2$ **19**	PhS $\diagdown$ **41**	**42a** **42b**	59:41	38

[a] Diastereomeric ratios were determined by ^{1}H NMR analysis of crude mixtures. [b] Isolated yields are listed. [c] Numbers in parentheses represent yields obtained by using 1.00:1.05:10.0 ratio of amine:aldehyde:dienophile and 10 mol% catalyst.

94

the parent 3-aminocoumarin (**17**). However, attempted variation of the 3-aminocoumarin component resulted in poor yields (Entries 8-11, Table 2.2). In most cases, small amounts of one or more side products were observed by tlc analysis and were even isolated during chromatography. However, their ^{1}H NMR spectra were complex and could not be reasonably interpreted. Their mass spectra were also complicated, but often contained major signals corresponding to M-2 or M-4 for the Povarov adducts. Some intractable materials were also generated. Self-reaction of the *in situ* formed azadienes may be responsible for this result.[29]

2.2.3 Study of the Effect of Various Parameters on the One-pot Povarov Reaction

At this stage, other parameters, *i.e.* the effect of catalyst loading, ratios of the reactants and the effect of concentration on the yield, were investigated. For this purpose, a reaction having the following features was desired: 1) the two diastereomeric products should be easily separable from other side products by flash chromatography, 2) the reaction time should be short, and 3) the aldehyde should be commercially available. The reaction between 3-aminocoumarin (**17**), 2-naphthaldehyde (**23**) and 3 equiv of DHP (Entry 1, Table 2.3) again met these criteria. The yield of the Povarov adducts was considerably improved (74%) when 10 mol% Yb(OTf)$_3$ was used (Entry 2, Table 2.3). A further increase in the catalyst loading did not improve the yields (Entries 3 and 4, Table 2.3). Increasing the number of equivalents of DHP to 5 and then 10 resulted in an increase in the yield of the Povarov adducts (84% and 89%, Entries 5 and 6, respectively, Table 2.3). A further increase in the number of equivalents of the dienophile did not have

TABLE 2.3 Effect of Catalyst Loading, Concentration of **17** and Equivalents of

Dienophile on the Yield
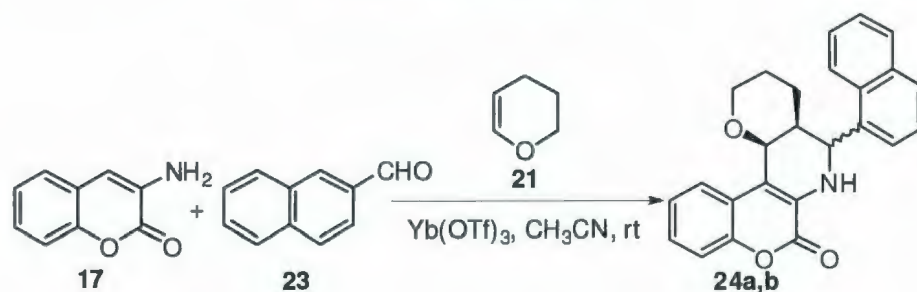
Entry	Yb(OTf)$_3$ mol%	Concentration of **17**, equivalents of dienophile (equiv)	*endo/exo* ratio[a]	Combined Yield (%)[b]
1	5	0.10 M, 3.0	21:79	56
2	10	0.10 M, 3.0	26:74	74
3	15	0.10 M, 3.0	18:82	72
4	20	0.10 M, 3.0	24:76	71
5	10	0.10 M, 5.0	22:78	84
6	10	0.10 M, 10.0	21:79	89
7	10	0.10 M, 15.0	19:81	87
8	10	0.10 M, 20.0	22:78	86
9	10	0.05 M, 10.0	22:78	89
10	10	0.25 M, 10.0	21:79	88
11	10	0.50 M, 10.0	21:79	84

[a] Diastereomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. [b] Isolated yields.

any further beneficial effect on the yield (Entries 7 and 8, Table 2.3). Also, the yields were not significantly affected by the changes in concentration of 3-aminocoumarin (**17**) (Entries 9-11, Table 2.3). Thus, a few of the reactions listed in Table 2.2 were repeated with the new reaction conditions, *i.e.* a 1.00:1.05:10.0 ratio of 3-aminocoumarin:aldehyde:dienophile with 10 mol% Yb(OTf)$_3$. The observation that the yield increased in two cases (Entries 1 and 9, Table 2.2) and decreased in two cases (Entries 10 and 11, Table 2.2) suggested that optimal conditions are somewhat case-specific for the one-pot Povarov reaction.

To ascertain whether the Povarov adducts can equilibrate, *endo* diastereomer **32a** was resubjected to the original reaction conditions, *i.e.* 5 mol% Yb(OTf)$_3$ in acetonitrile. No signs of conversion to the *exo* diastereomer (**32b**) were observed at room temperature (3 hours) or after 24 hours at reflux. Also, the ratio of a 50:50 mixture of diastereomers **32a,b** did not change when the mixture was heated to reflux in acetonitrile in the presence of 5 mol% Yb(OTf)$_3$. These results suggest that either the tautomerization step is not reversible under these conditions or that the tautomerization is reversible and the IEDDA reaction, whether concerted or stepwise,[6b] is not. Finally, X-ray quality crystals for *exo* diastereomer **24b** were obtained. A single crystal X-ray structure determination confirmed that the NMR-based assignments of the relative stereochemistry were correct (Fig. 2.1).
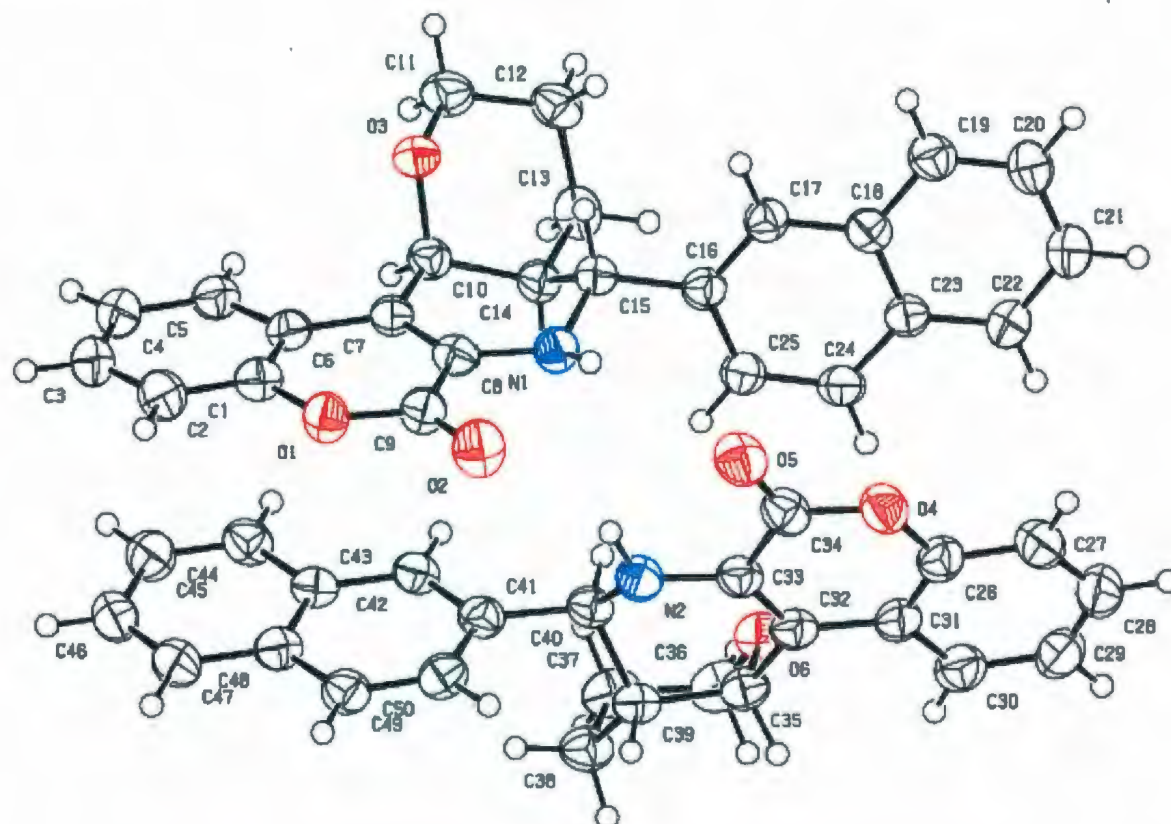
FIGURE 2.1 ORTEP Representation of X-ray Crystal Structure of **24b**

(The numbering in the above figure is different than numbering for **24b**, elsewhere in this

chapter)

2.2.4 Chemistry of Povarov Adducts

With a set of relatively complex molecules (tricyclic and tetracyclic heterocycles
with 2-3 stereogenic centers) in hand, some aspects of their chemistry were then
investigated.   Access to free hydroxy or carboxylic acid functional groups might be
useful for water solubility and further synthetic transformations.   In this context,
compound **35a** was chemoselectively hydrolyzed with K_2CO_3/MeOH to afford phenol **43**

in 72% yield (Scheme 2.9). Similarly, ester **28b** was chemoselectively hydrolyzed to afford carboxylic acid **44** in 99% yield. Interestingly, when **28b** was subjected to anydrous demethylation conditions, *i.e.* TMSCl/NaI,[30] the desired carboxylic acid **44** was not formed. After heating at 50 °C in DMF for 18 hours and then 150 hours at 90 °C, 10% of the starting material **28b** was recovered after flash chromatography along with two new products. One of the products was pyrido[2,3-*c*]coumarin **45** (R = H), which was presumably formed by an elimination/dehydrogenation process. It was then hydrolyzed with 10 M KOH to afford the ring opened terphenyl-type product **47** (Scheme 2.10). The other new product was the formate ester **46** (R = CHO), which could form from **45**, or one of its precursors, via a Vilsmeier-Haack-like formylation.

SCHEME 2.9 Reactions of Povarov Adducts **35a** and **28b**
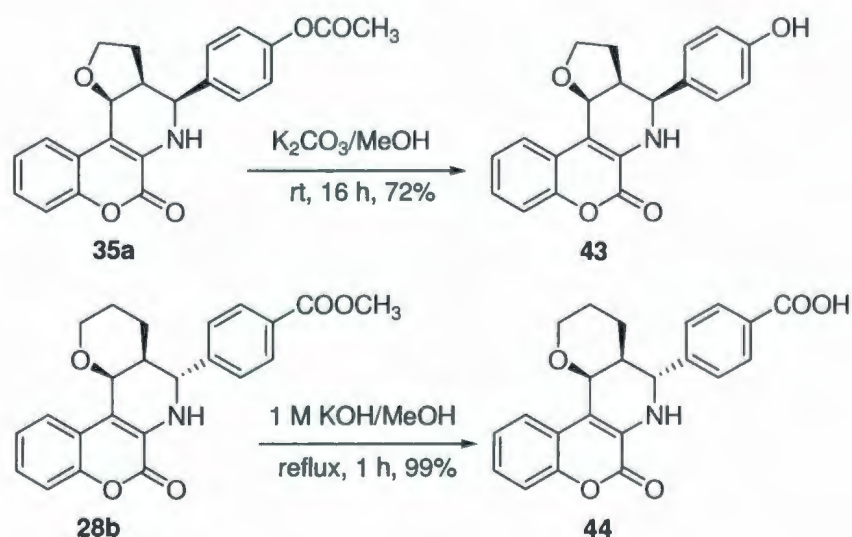
SCHEME 2.10 Synthesis of a Terphenyl-type Compound **47**

28b

TMSCl, NaI
DMF, 50 °C, 18 h
then 90 °C, 6 d
23%

45, R = H, 23%
46, R = CHO, 30%

10 M aq. KOH
16 h, 66%

47
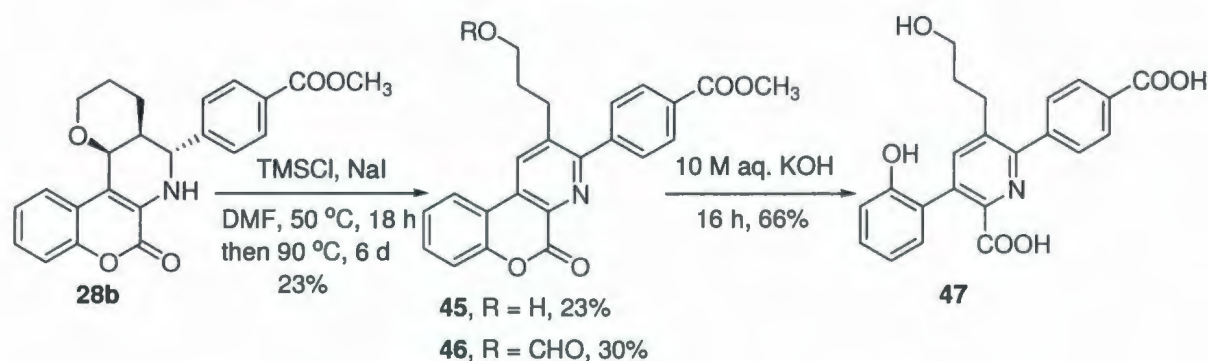
The observation that Povarov adduct **28b** could be converted into the corresponding pyrido[2,3-c]coumarin, a rather uncommon heteroaromatic system,[31] provided incentive to investigate more efficient ways of achieving this transformation. The treatment of Povarov adducts with an oxidizing agent, *e.g.* bromine, would be expected to bring about aromatization of the nitrogen-containing ring through a series of addition and elimination reactions.[32] Accordingly, **28b** was reacted with Br_2 in the dark. Aromatized product **45** was isolated in 61% yield after 1 h. An internal elimination reaction, which opened the tetrahydropyran ring, occurred during the aromatization process. Similarly, Povarov adducts **35a,b** were converted into the corresponding pyrido[2,3-c]coumarin **48** (80%), by the action of Br_2/CH_2Cl_2 in the dark (Scheme 2.11). However, only 9% and 39% yields of the pyrido[2,3-c]coumarins **49** and **50** were obtained from the reactions (Scheme 2.11) of Povarov adducts **32a,b** and **26a,b**, respectively. The low yields are presumably due to the presence of an additional coumarin unit, which may react unproductively with Br_2.[33]

Other aromatization methods were then screened. When compounds **32a,b** were

SCHEME 2.11 Aromatization of Povarov Adducts

28b; R = COOCH$_3$, n = 2
35a,b; R = OCOCH$_3$, n = 1

45; R = COOCH$_3$, n = 2; 61%
48; R = OCOCH$_3$, n = 1; 80%

32a,b; n = 1
26a,b; n = 2

49; n = 1, 9%
50; n = 2, 39%
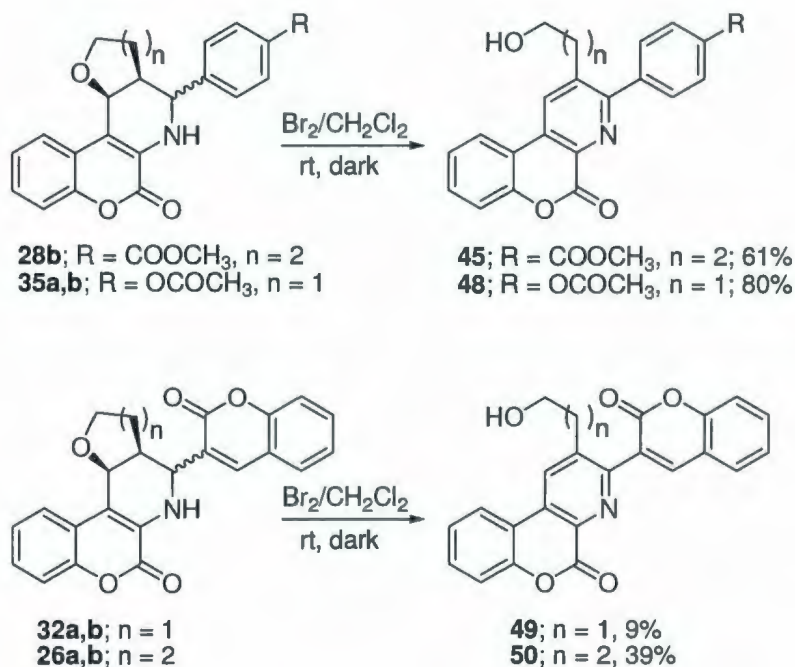
refluxed with Pd/C in xylenes, the reaction was very sluggish. Only traces of the pyrido[2,3-*c*]coumarin **49** were observed by tlc analysis after 6 days at reflux. Acetic acid has been known to accelerate such dehydrogenations.[34] Therefore, the dehydrogenation was attempted with acetic acid as the solvent. Again, only traces of the product were observed (tlc analysis) under these conditions. Another commonly used reagent for carrying out dehydrogenations is DDQ.[35] Heating the Povarov adducts **32a,b** with DDQ in benzene at reflux afforded pyrido[2,3-*c*]coumarin **49** and traces of another product, which could not be obtained in pure form. ^{1}H NMR and LC/MS analysis of this impure and poorly soluble compound were consistent with the aromatized compound **51**

101

(Fig. 2.2).

51
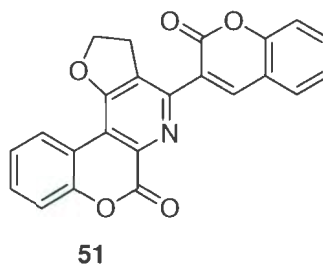
FIGURE 2.2 A possible side product **51** from conversion of **32a,b** to **49** using DDQ

Following a procedure by Hartmann *et al.*,[36] in which nitrous gases (obtained by dropwise addition of 6 M NaNO$_2$ solution to conc. HCl) were used for preparation of 1,2,4,5-tetrazines from corresponding dihydrotetrazines, a stream of nitrous gases was passed through a solution of **32a,b** in CH$_2$Cl$_2$. Gratifyingly, the desired product **49** was formed in 90% yield. Other oxidizing agents *i.e.* MnO$_2$[37] and CAN,[38] also delivered **49**, but the yields were lower (MnO$_2$: 24% and CAN: 21%) and the reactions were considerably slower. Disappointingly, the nitrous gases, when employed for the conversion of **28b** into **45** afforded only 10% yield.

Povarov adducts formed by using phenyl vinyl sulfide as a dienophile, have been converted into quinolines by an oxidation (NaIO$_4$) and thermolysis of the resulting sulfoxide.[39] Treatment of **42a,b** with NaIO$_4$ at room temperature did not show any signs of reaction (by tlc). However, pyrido[2,3-*c*]coumarin **53** was obtained when the reaction mixture was heated at reflux for 23 hours. Presumably, the first step in this conversion is the oxidation of the sulfide to the sulfoxide **52**, which then undergoes a *syn* elimination

reaction (Scheme 2.12). The resulting diene is then oxidized to form the aromatized product.

SCHEME 2.12 Synthesis of **53** by Oxidation/*syn* Elimination/Dehydrogenation
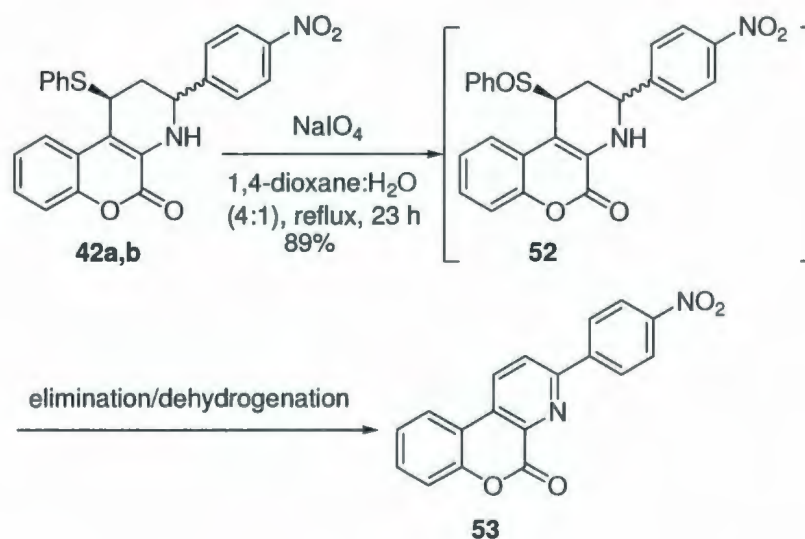
2.3 Conclusion

In conclusion, *in situ*-generated 2-azadienes derived from the condensation of 3-aminocoumarins and aromatic aldehydes take part in the Povarov reaction to afford 1,2,3,4-tetrahydropyrido[2,3-*c*]coumarins. The available evidence points toward a concerted asynchronous IEDDA cycloaddition rather than a stepwise cyclization during the Povarov reaction. The multicomponent version of this reaction provides rapid access to unusual tricyclic and tetracyclic heterocycles. The corresponding pyrido[2,3-

c]coumarins can be formed upon oxidation of the Povarov adducts with various oxidizing agents. Further applications of this methodology to the synthesis of complex heterocycles will be discussed in the following chapter.

2.4 Experimental Section

2.4.1 General Methods

All reactions were carried out without inert gas protection, unless otherwise mentioned. THF was dried and distilled over sodium/benzophenone. All other chemicals, including solvents, were used as received, without further purification. Thin layer chromatography (tlc) was performed on MN PolyGram precoated silica gel plates using 254 nm UV visualization. Flash chromatography was performed on silica gel columns. Melting points were recorded on Fisher-Johns apparatus and are uncorrected. All new compounds were characterized by ^1H NMR, ^{13}C NMR, COSY, HMQC, HMBC, IR and HRMS techniques. ^1H and ^{13}C NMR spectra were recorded on Bruker AVANCE spectrometer at 500.133 MHz and 125.770 MHz, respectively. Peaks reported are relative to internal standards: TMS ($\delta = 0.00$) for ^1H and CDCl$_3$ ($\delta = 77.23$) or DMSO-d_6 ($\delta = 39.51$) for ^{13}C spectra. ^1H NMR signals for H-5 protons in the Povarov adducts were used for the determination of diastereomeric ratio of Povarov adducts. Reported multiplicities are apparent. Infrared spectra were obtained on Bruker Tensor 27 instrument using neat samples. Low-resolution mass spectra were obtained using using Agilent 1100 series LC/MS chromatographic system and high-resolution mass spectra were obtained using Waters GCT Permier Micromass mass spectrometer.using neat samples. X-ray crystal structure was obtained on AFC8-Saturn single crystal X-ray diffractometer by Julie. Collins, C-CART.

2.4.2 General Experimental Procedures

2.4.2.1 General Experimental Procedure A: Preparation of Povarov adducts using the three-component reaction

To a clear, colorless solution of 3-aminocoumarin in acetonitrile (~ 0.1 M solution) were added the aldehyde (1.05 equiv), Yb(OTf)$_3$ (5 mol %) and the dienophile (3.0 equiv). The reaction mixture was stirred at room temperature or heated at reflux as specified. The reaction was monitored by tlc until the complete consumption of 3-aminocoumarin occured. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography. The isolated product was then recrystallized from the appropriate solvent(s). The *dr* was determined from ^{1}H NMR analysis of the crude reaction mixture.

2.4.2.2 General Experimental Procedure B: Preparation of Povarov adducts using modified conditions for the three-component reaction

To a clear, colorless solution of 3-aminocoumarin in acetonitrile (~ 0.1 M solution) were added the aldehyde (1.05 equiv), Yb(OTf)$_3$ (10 mol %) and the dienophile (3.0 equiv). The reaction mixture was stirred at room temperature or heated at reflux as specified for individual reactions. The reaction was monitored by tlc until the complete consumption of 3-aminocoumarin occured. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography. The isolated product

was then recrystallized from the appropriate solvent(s). The *dr* was determined from ^{1}H NMR analysis of the crude reaction mixture.

2.4.2.3 General Experimental Procedure C: Preparation of pyrido[2,3-*c*]coumarins

To a clear, pale yellow solution of Povarov adducts (~ 1:1 ratio of *endo* and *exo* diastereomers) in dichloromethane (~ 0.1 M solution) was added Br$_2$ (1.0 M solution in dichloromethane, 2.0 equiv). This solution was stirred in the dark at room temperature until the Povarov adducts were totally consumed. The reaction mixture was diluted with ethyl acetate (5.0 mL) and washed with aqueous NaHSO$_4$ followed by brine. The organic solution was then dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography to afford the corresponding pyrido[2,3-*c*]coumarin.

2.4.3 Synthesis and Characterization for Individual Compounds

(4a*S**,5*S**,12c*S**)-5-(4-Nitrophenyl)-3,4,4a,5,6,12c-hexahydro-2*H*-1,8-dioxa-6-aza-

benzo[*c*]phenanthren-7-one   (22a)   and   (4a*S**,5*R**,12c*S**)-5-(4-nitrophenyl)-

3,4,4a,5,6,12c-hexahydro-2*H*-1,8-dioxa-6-aza-benzo[*c*]phenanthren-7-one (22b)

22a   **22b**
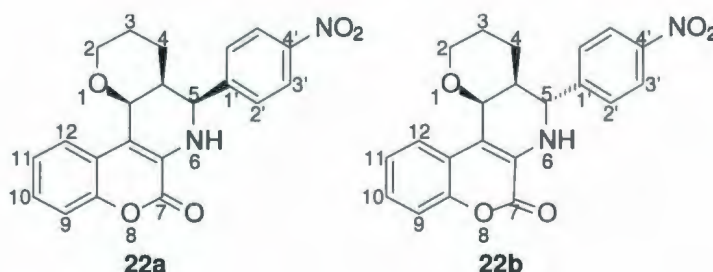
Following general experimental procedure A, 3-aminocoumarin (**17**) (0.161 g, 1.0

mmol), 4-nitrobenzaldehyde (**19**) (0.159 g, 1.05 mmol), Yb(OTf)$_3$ (0.031 g, 5.0 mol%)

and DHP (0.27 mL, 3.0 mmol) in acetonitrile (10 mL) were reacted at room temperature

for 24 h. The reaction mixture remained a clear yellow solution (after the addition of

dienophile) over the course of the reaction. The solvent was removed under reduced

pressure to afford a yellow residue and the *dr* was determined to be 36:64 in favor of the

exo isomer. The residue was then subjected to flash chromatography (dichloromethane)

to afford **22a** as a white solid (0.041 g, 11%), **22b** as a white solid (0.094 g, 25%) and a

mixed fraction (0.015 g, 4%). Combined yield = 0.15 g, 40%.

22a: mp = 228-229 °C (chloroform/hexane). δ_H(CDCl$_3$) = 8.27 (d, 2H, *J* = 9.1 Hz, H-3'),

8.21 (d, 1H, *J* = 7.6 Hz, H-12), 7.63 (d, 2H, *J* = 8.7 Hz, H-2'), 7.37-7.34 (m, 2H), 7.30-

7.28 (m, 1H), 5.50 (d, 1H, J = 4.7 Hz, H-12c), 5.07 (s, 1H, H-6), 4.81 (d, 1H, J = 2.5 Hz, H-5), 3.65-3.64 (m, 1H, H-2α), 3.25 (td, 1H, J = 11.0, 1.2 Hz, H-2β), 2.38-2.35 (m, 1H, H-4a), 1.76-1.67 (m, 1H), 1.59-1.48 (m, 1H), 1.43-1.41 (m, 2H) ppm; δ_C(CDCl$_3$) = 158.5 (C-7), 148.5, 147.9, 147.2, 130.7, 128.0 (C-3'), 127.1, 125.1, 124.8 (C-12), 124.1 (C-2'), 120.3, 116.7, 116.6, 71.8 (C-12c), 62.9 (C-2), 58.9 (C-5), 38.3 (C-4a), 24.3 (C-3), 19.7 (C-4) ppm; IR ν = 3340 (w), 2854 (w), 1722 (s), 1618 (w), 1598 (w), 1516 (m), 1348 (s), 1181 (m), 1091 (s), 857 (m), 752 (s) cm^{-1}. HRMS m/z [M$^+$] calcd for C$_{21}$H$_{18}$N$_2$O$_5$ 378.1214, found 378.1225. **22b:** mp = 263-264 °C (chloroform/hexane). δ_H(CDCl$_3$) = 8.27 (d, 2H, J = 9.4 Hz, H-3'), 7.62 (d, 2H, J = 8.2 Hz, H-2'), 7.57-7.55 (m, 1H, H-12), 7.29-7.27 (m, 3H), 5.09 (s, 1H, H-6), 4.87 (d, 1H, J =11.4 Hz, H-5), 4.71 (d, 1H, J = 3.5 Hz, H-12c), 4.20-4.17 (m, 1H, H-2α), 3.82 (td, 1H, J = 11.6, 1.7 Hz, H-2β), 2.12-2.08 (m, 1H, H-4a), 1.94-1.78 (m, 2H), 1.48-1.46 (m, 2H) ppm; δ_C(CDCl$_3$) = 158.9 (C-7), 148.6, 148.3, 147.9, 130.0 (C-2'), 129.0, 126.8, 125.1, 124.3 (C-3'), 122.0, 120.3, 116.8, 115.4, 69.7 (C-12c), 69.3 (C-2), 54.2 (C-5), 38.9 (C-4a), 23.6 (C-3), 22.0 (C-4) ppm; IR ν = 3389 (w), 2946 (w), 1710 (s), 1633 (m), 1509 (s), 1341 (s), 1186 (m), 1090 (m), 752 (s) cm^{-1}. HRMS m/z [M$^+$] calcd for C$_{21}$H$_{18}$N$_2$O$_5$ 378.1214, found 378.1230.

(4a*S**,5*S**,12c*S**)-5-Naphthalen-2-yl-3,4,4a,5,6,12c-hexahydro-2*H*-1,8-dioxa-6-aza-benzo[*c*]phenanthren-7-one (24a) and (4a*S**,5*R**,12c*S**)-5-Naphthalen-2-yl-3,4,4a,5,6,12c-hexahydro-2*H*-1,8-dioxa-6-aza-benzo[*c*]phenanthren-7-one (24b)
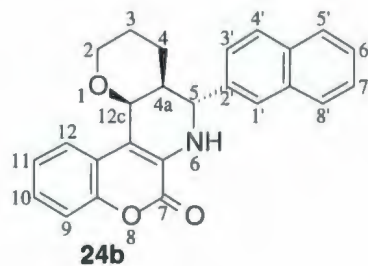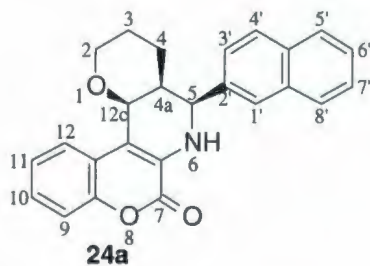
Following general experimental procedure B, 3-aminocoumarin (**17**) (0.32 g, 2.0 mmol), 2-naphthaldehyde (0.33 g, 2.1 mmol) and DHP (0.54 mL, 6.0 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.062 g, 5.0 mol%) in acetonitrile (20 mL) at room temperature for 5 min. The reaction mixture remained a clear pale yellow solution (after the addition of dienophile) over the course of the reaction. The solvent was removed under reduced pressure to afford a yellow residue and the *dr* was determined to be 21:79 in favor of the *exo* isomer. The residue was then subjected to flash chromatography (0-5% ethyl acetate/hexanes) to afford **24a** as a white solid (0.06 g, 8%), **24b** as a white solid (0.21 g, 28%) and a mixed fraction (0.15 g, 20%). Combined yield = 0.42 g, 56%

24a: mp = 201-202 °C (chloroform/hexane); δ_H(CDCl$_3$) = 8.26 (d, *J* = 7.4 Hz, 1H), 7.91 (s, 1H), 7.88-7.85 (m, 3H), 7.54-7.47 (m, 3H), 7.34-7.31 (m, 2H), 7.30-7.26 (m, 1H), 5.57 (d, *J* = 5.9 Hz, 1H, H-12c), 5.18 (s, 1H, H-6), 4.87 (d, *J* = 2.1 Hz, 1H, H-5), 3.65-3.62 (m, 1H, H-2), 3.22-3.18 (m, 1H, H-2), 2.42-2.40 (m, 1H, H-4a), 1.73-1.66 (m, 1H,),

110

1.57-1.51 (m, 1H), 1.47-1.42 (m, 2H) ppm; δ_C(CDCl$_3$) = 158.6 (C-7), 148.3, 136.9, 133.4, 133.2, 131.3, 128.6, 128.1, 127.9, 126.7, 126.6, 126.3, 125.5, 125.03, 124.96, 124.8, 120.7, 116.5, 115.8, 72.2 (C-12c), 62.5 (C-2), 59.3 (C-5), 38.5 (C-4a), 24.6, 19.5 ppm; IR ν = 3348 (m), 1686 (s), 1595 (m), 1563 (m), 1501 (m), 1449 (w), 1347 (w), 1317 (w), 1264 (w), 1204 (m), 1186 (m), 1104 (w), 1087 (s) cm^{-1}; MS (APCI) m/z (relative intensity) = 384 (M$^+$+1, 55), 382 (100), 380 (61), 376 (13). HRMS [M$^+$] calcd for C$_{25}$H$_{21}$NO$_3$ 383.1521, found 383.1526. **24b:** mp = 240-241 °C (chloroform/hexane); δ_H(CDCl$_3$) = 7.91-7.85 (m, 4H), 7.58 (dd, J = 8.5, 2.0 Hz, 1H), 7.54-7.50 (m, 3H), 7.30-7.27 (m, 3H), 5.19 (s, 1H, H-6), 4.94 (d, J = 11.0 Hz, 1H, H-5), 4.75 (d, J = 2.6 Hz, 1H, H-12c), 4.20 (dd, J = 11.4, 3.7 Hz, 1H, H-2), 3.83 (m, 1H, H-2), 2.21 (m, 1H, H-4a), 2.02-1.95 (m, 1H), 1.81-1.74 (m, 1H), 1.59-1.56 (m, 1H), 1.44-1.41 (m, 1H) ppm; δ_C(CDCl$_3$) = 159.1 (C-7), 148.4, 137.7, 133.6, 133.5, 130.4, 129.1, 128.1, 128.0, 127.6, 126.7, 126.5, 126.2, 125.2, 125.0, 121.9, 120.8, 116.7, 114.5, 70.1 (C-12c), 69.4 (C-2), 54.7 (C-5), 38.5 (C-4a), 23.7, 22.1 ppm; IR ν = 3363 (m), 1700 (s), 1626 (m), 1603 (w), 1572 (w), 1507 (m), 1473 (w), 1450 (w), 1357 (w), 1320 (m), 1285 (w), 1255 (w), 1215 (m), 1198 (m), 1181 (m), 1125 (w), 1062 (s) cm^{-1}; MS (APCI) m/z (relative intensity) = 384 (M$^+$+1, 100), 383 (24), 382 (58), 380 (21), 376 (17). HRMS [M$^+$] calcd for C$_{25}$H$_{21}$NO$_3$ 383.1521, found 383.1519.

Following general experimental procedure B, 3-aminocoumarin (**17**) (0.081 g, 0.50 mmol), 2-naphthaldehyde (0.083 g, 0.53 mmol) and DHP (0.14 mL, 1.5 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.031 g, 10 mol%) in acetonitrile (5 mL) at room temperature for 5 min. The reaction mixture remained a clear pale yellow solution (after

the addition of dienophile) over the course of the reaction. The solvent was removed under reduced pressure to afford a yellow residue and the *dr* was determined to be 18:82 in favor of the *exo* isomer. The residue was then subjected to flash chromatography (10% ethyl acetate/hexanes) to afford **24a,b** as a white solid (0.17 g, 89%).

(4a*S**, 5*S**, 12c*S**)-5-(2-Oxo-2*H*-chromen-3-yl)-3,4,4a,5,6,12c-hexahydro-2*H*-1,8-dioxa-6-aza-benzo[*c*]phenanthren-7-one (26a) and (4a*S**, 5*R**, 12c*S**)-5-(2-Oxo-2*H*-chromen-3-yl)-3,4,4a,5,6,12c-hexahydro-2*H*-1,8-dioxa-6-aza-benzo[*c*]phenanthren-7-one (26b)
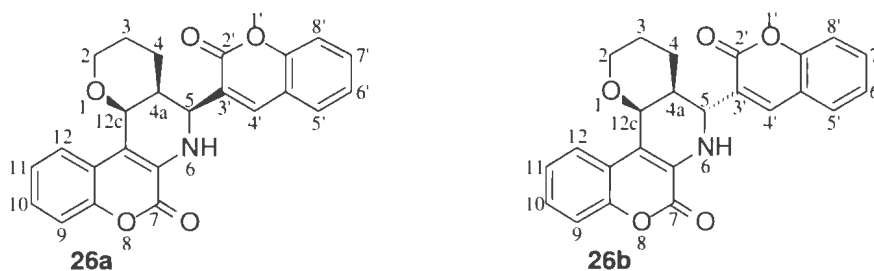
26a   **26b**

Following general experimental procedure B, 3-aminocoumarin (**17**) (0.32 g, 2.0 mmol), 3-formylcoumarin (**25**) (0.37 g, 2.1 mmol) and DHF (0.54 mL, 6.0 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.062 g, 5.0 mol%) in acetonitrile (20 mL) at room temperature for 30 min. The clear pale yellow solution turned into a thick pale yellow suspension (after 5 min) and again into a clear yellow solution over the course of the reaction. A yellow residue was obtained and the *dr* was determined to be 36:64 in favor of the *exo* isomer. The residue was then subjected to flash chromatography (0-5% ethyl

acetate/hexanes) to afford **26a** as a white solid (0.14 g, 17%), **26b** as a white solid (0.27 g, 34%) and a mixed fraction (0.15 g, 19%). Combined yield = 0.57 g, 71%.

26a: mp = 224-225 °C (chloroform/hexane); δ_H(CDCl$_3$) = 8.28 (d, J = 8.0 Hz, 1H), 7.97 (s, 1H, H-4′), 7.58-7.55 (m, 2H), 7.38 (d, J = 9.0 Hz, 1H), 7.34-7.33 (m, 3H), 7.29-7.27 (m, 1H), 5.53 (d, J = 5.0 Hz, 1H, H-12c), 4.86 (s, 1H, H-5), 4.75 (s, 1H, H-6), 3.66 (dd, J = 11.0 Hz, J = 2.0 Hz, 1H, H-2), 3.18 (t, J = 11.5 Hz, 1H, H-2), 2.66 (m, 1H, H-4a), 1.68-1.66 (m, 2H, H-3), 1.64-1.62 (m, 2H, H-4) ppm; δ_C(CDCl$_3$) = 160.3 (C-2′), 158.6 (C-7), 153.3, 148.4, 139.4 (C-4′), 135.4, 134.4, 131.9, 130.8, 130.5, 128.2, 127.1, 126.8, 125.0, 120.3, 118.8, 117.6, 116.6, 71.7 (C-12c), 62.5 (C-2), 53.8 (C-5), 33.8 (C-4a), 24.6 (C-3), 19.9 (C-4) ppm; IR ν = 3370 (m), 1712 (s), 1621 (w), 1607 (w), 1501 (m), 1448 (w), 1386 (w), 1356 (w), 1341 (w), 1317 (m), 1282 (w), 1255 (m), 1204 (m), 1174 (w), 1113 (m), 1087 (s), 1051 (s), 1021 (w) cm^{-1}; MS (APCI) m/z (relative intensity) = 402 (M$^+$+1, 100), 400 (19), 398 (32). HRMS [M$^+$] calcd for C$_{24}$H$_{19}$NO$_5$ 401.1263, found 401.1255.

26b: mp = 267-269 °C (chloroform/hexane); δ_H(CDCl$_3$) = 7.94 (s, 1H, H-4′), 7.64-7.62 (m, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.33-7.27 (m, 4H), 5.10 (d, J = 9.6 Hz, 1H, H-5), 4.97 (s, 1H, H-6), 4.70 (d, J = 3.0 Hz, 1H, H-12c), 4.08 (d, J = 10.2 Hz, 1H, H-2), 3.78 (td, J = 11.2 Hz, J = 2.4 Hz, 1H, H-2), 2.20 (m, 2H), 1.94-1.87 (m, 1H), 1.79-1.76 (m, 1H), 1.52-1.49 (m, 1H) ppm; δ_C(CDCl$_3$) = 161.0 (C-2′), 159.0 (C-7), 153.6, 148.5, 141.3, 132.3, 130.1, 129.3, 128.2, 126.7, 125.1, 124.9, 122.4, 120.4, 119.1, 116.7, 115.3, 69.8 (C-12c), 68.7 (C-2), 49.1 (br, C-5), 38.8 (br), 24.3, 22.3 ppm; IR ν = 3380 (m), 1714 (s), 1701 (s), 1653 (m), 1632 (m), 1609 (m), 1575 (m), 1558 (w), 1504 (m), 1474 (m), 1463 (m), 1448 (w), 1402 (w), 1377 (w), 1340 (w),

1319 (m), 1282 (w), 1262 (w), 1245 (w), 1224 (w), 1185 (m), 1138 (w), 1123 (w), 1098 (w), 1068 (m), 1060 (m), 1007 (w) cm^{-1}; MS m/z (relative intensity) = 388 (M$^+$+1, 100), 386 (61), 384 (34), 369 (14), 368 (60), 356 (60). HRMS [M$^+$] calcd for $C_{24}H_{19}NO_5$ 401.1261, found 401.1259.

(4a*S**, 5*R**,12c*S**)-4-(7-Oxo-2,3,4,4a,5,6,7,12c-octahydro-1,8-dioxa-6-aza-benzo[*c*]phenanthren-5-yl)benzoic acid methyl ester (28b)

28b
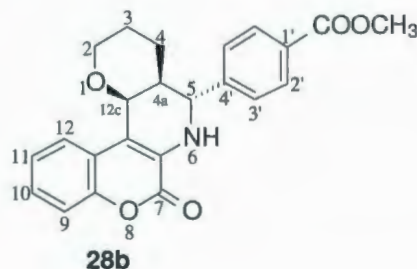
Following general experimental procedure B, 3-aminocoumarin (**17**) (1.77 g, 11.0 mmol), methyl 4-formylbenzoate (**27**) (1.90 g, 11.6 mmol) and DHF (3.02 mL, 33.0 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.34 g, 5.0 mol%) in acetonitrile (125 mL) at room temperature for 23 h. The thick pale yellow suspension turned into a clear yellow solution after 5 min. A yellow residue was obtained and the *dr* was determined to be <5:95 in favor of the *exo* isomer. The residue was then subjected to flash chromatography (dichloromethane) to afford **28b** as a white solid (2.32 g, 54%).

mp = 206-207 °C (chloroform/hexane). δ$_H$(CDCl$_3$) = 8.08 (d, 2H, *J* = 7.6 Hz, H-2'), 7.57-7.55 (m, 1H, H-12), 7.56 (d, 2H, *J* = 7.3 Hz, H-3'), 7.30-7.25 (m, 3H), 5.11 (s, 1H, H-6),

4.82 (d, 1H, J = 11.5 Hz, H-5), 4.70 (d, 1H, J = 3.4 Hz, H-12c), 4.19-4.16 (m, 1H, H-2), 3.94 (s, 3H, COOCH_3), 3.81 (td, 1H, J = 11.9, 2.1 Hz, H-2), 2.11-2.08 (m, 1H, H-4a), 1.93-1.87 (m, 1H), 1.82-1.75 (m, 1H), 1.62-1.60 (m, 1H), 1.50 (m, 1H), 1.44 (m, 1H,) ppm; δ_C(CDCl$_3$) = 166.8 (COOCH$_3$), 159.0 (C-7), 148.4, 145.6, 130.6, 130.6, 130.38, 130.35, 130.2 (C-2'), 126.4 (H-12), 125.0, 120.6 (C-3'), 116.7, 114.8, 69.9 (C-12c), 69.3 (C-2), 54.43 (C-5), 54.35 (COOCH_3), 38.7 (C-4a), 23.7, 22.0 ppm; IR ν = 3400 (w), 2844 (w), 1714 (s), 1704 (s), 1506 (w), 1279 (m), 1058 (m), 783 (s) cm^{-1}. HRMS m/z [M$^+$] calcd for C$_{23}$H$_{21}$NO$_5$ 391.1420, found 391.1424.

(4aS*, 5R*, 12cS*)-Acetic acid 4-(7-oxo-2,3,4,4a,5,6,7,12c-octahydro-1,8-dioxa-6-aza-benzo[c]phenanthren-5-yl)-phenyl ester (30b)

Following general experimental procedure B, 3-aminocoumarin (**17**) (1.10 g, 6.80 mmol), 4-acetoxybenzaldehyde (**29**) (1.17 g, 7.14 mmol) and DHF (1.87 mL, 20.4 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.21 g, 5.0 mol%) in acetonitrile (100 mL) at reflux for 3.5 h. The thick pale yellow suspension turned into a clear yellow solution after 5 min. A yellow residue was obtained and dr was determined to be <5:95 in favor

of the *exo* isomer. The residue was then subjected to flash chromatography (dichloromethane) to afford **30b** as a white solid (0.69 g, 26%).

mp = 230-231 °C (chloroform/hexane). δ_H(CDCl$_3$) = 7.57-756 (m, 1H, H-12), 7.45 (d, 2H, J = 8.5 Hz, H-2'), 7.30-7.25 (m, 3H), 7.15 (d, 2H, J = 8.3 Hz, H-3'), 5.09 (s, 1H, H-6), 4.78 (d, 1H, J = 11.5 Hz, H-5), 4.71 (d, 1H, J = 2.8 Hz, H-12c), 4.20-4.16 (m, 1H, H-2β), 3.81 (td, 1H, J = 11.5, 2.2 Hz, H-2α), 2.33 (s, 3H, OCOCH_3), 2.09-2.06 (m, 1H, H-4a), 1.92-1.88 (m, 1H, H), 1.81-176 (m, 1H), 1.62-1.60 (m, 1H), 1.45-1.42 (m, 1H,) ppm; δ_C(CDCl$_3$) = 169.5 (OCOCH$_3$), 158.0 (C-7), 150.9, 148.4, 137.9, 130.3, 129.1 (C-2'), 126.3, 125.0, 122.2 (C-3'), 121.9 (C-12), 120.7, 116.7, 114.5, 70.1 (C-12c), 69.4 (C-2), 54.0 (C-5), 38.7 (C-4a), 24.4, 22.8, 21.4 ppm; IR ν = 3411 (w), 2937 (w), 2852 (w), 1717 (s), 1635 (m), 1507 (m), 1184 (s), 1061 (s), 1043 (s), 791 (s) cm^{-1}. HRMS m/z [M$^+$] calcd for C$_{23}$H$_{21}$NO$_5$ 391.1420, found 391.1406.

(3a*S**, 4*S**, 11c*S**)-4-(2-Oxo-2*H*-chromen-3-yl)-2,3,3a,4,5,11c-hexahydro-1,7-dioxa-5-aza-cyclopenta[*c*]phenanthren-6-one (32a) and (3a*S**, 4*R**, 11c*S**)-4-(2-Oxo-2*H*-chromen-3-yl)-2,3,3a,4,5,11c-hexahydro-1,7-dioxa-5-aza-cyclopenta[*c*]phenanthren-6-one (32b)

32a   32b

Following general experimental procedure B, 3-aminocoumarin (17) (0.32 g, 2.0 mmol), 3-formylcoumarin (25) (0.37 g, 2.1 mmol) and DHF (0.45 mL, 6.0 mmol) were reacted in the presence of Yb(OTf)₃ (0.062 g, 5.0 mol%) in acetonitrile (20 mL) at room temperature for 20 min. The clear pale yellow solution turned into a thick pale yellow suspension over the course of the reaction. The solvent was removed under reduced pressure to afford a yellow residue and *dr* was determined to be 42:58 in favor of the *exo* isomer. The residue was then subjected to flash chromatography (0-3% ethyl acetate/hexanes) to afford 32a as a white solid (0.13 g, 17%), 32b as a white solid (0.23 g, 29%) and a mixed fraction (0.09 g, 12%). Combined yield = 0.45 g, 58%.

32a: mp = 248-249 °C (dichloromethane); δ_H(CDCl₃) = 8.10 (s, 1H, H-4′), 7.85 (d, *J* = 7.7 Hz, 1H), 7.59-7.56 (m, 2H), 7.40-7.30 (m, 5H), 5.50 (d, *J* = 7.1 Hz, 1H, H-11c), 4.87 (d, *J* = 1.7 Hz, 1H, H-4), 4.69 (s, 1H, H-5), 3.89 (td, *J* = 7.9, 2.3 Hz, 1H, H-2), 3.85-3.80

(m, 1H, H-2), 3.40-3.35 (m, 1H, H-3a), 2.10-2.01 (m, 1H, H-3), 1.73-1.67 (m, 1H, H-3)

ppm; δ_C(CDCl$_3$) = 160.4 (C-2′), 159.0 (C-6), 153.3, 149.0, 138.8 (C-4′), 132.1, 129.4,

128.3, 128.2, 127.6, 125.1, 125.0, 124.8, 120.2, 120.0, 119.0, 116.9, 116.6, 72.4 (C-11c),

67.4 (C-2), 51.8 (C-4), 41.1 (C-3a), 25.6 (C-3) ppm; IR ν = 3371 (m), 1715 (s), 1702 (s),

1638 (m), 1611 (m), 1578 (w), 1508 (m), 1469 (m), 1451 (m), 1399 (w), 1372 (w), 1342

(w), 1324 (m), 1282 (w), 1260 (w), 1248 (w), 1223 (w), 1282 (m), 1131 (w), 1123 (w),

1097 (w), 1077 (m), 1044 (m), 1005 (w); MS (APCI) m/z (relative intensity) = 388

(M$^+$+1, 100), 386 (33), 384 (21), 369 (21), 368 (84), 356 (14). HRMS [M$^+$] calcd for

C$_{23}$H$_{17}$NO$_5$ 387.1107, found 387.1100. **32b**: mp = 258-259 °C (dichloromethane);

δ_H(CDCl$_3$) = 7.89 (s, 1H, H-4′), 7.77 (d, J = 6.1 Hz, 1H), 7.57 (t, J = 7.9 Hz, 1H), 7.52 (d,

J = 7.2 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.33-7.27 (m, 4H), 5.20 (s, 1H, H-5), 4.81 (d, J

= 5.3 Hz, 1H, H-11c), 4.38 (d, J = 9.3 Hz, 1H, H-4), 4.13 (dd, J = 14.9, 8.0 Hz, 1H, H-2),

3.98 (dd, J = 14.2 Hz, 8.1 Hz, 1H, H-2), 2.73-2.72 (m, 1H, H-3a), 2.30-2.23 (m, 1H, H-

3), 2.07-2.05 (m, 1H, H-3) ppm; δ_C(CDCl$_3$) = 161.3 (C-2′), 158.8 (C-6), 153.6, 148.5,

141.2 (C-4′), 132.4, 130.0, 128.4, 128.3, 127.1, 125.1, 125.0, 123.6, 120.8, 119.0, 116.9,

116.7, 116.6, 72.3 (C-11c), 66.2 (C-2), 51.0 (C-4), 42.3 (C-3a), 28.7 (C-3) ppm; IR ν =

3380 (m), 1716 (s), 1704 (s), 1626 (m), 1609 (m), 1573 (w), 1505 (m), 1473 (m), 1453

(m), 1398 (w), 1376 (w), 1341 (w), 1321 (m), 1281 (w), 1259 (w), 1243 (w), 1220 (w),

1283 (m), 1135 (w), 1123 (w), 1099 (w), 1073 (m), 1045 (m), 1006 (w) cm^{-1}; MS (APCI)

m/z (relative intensity) = 388 (M$^+$+1, 100), 386 (61), 384 (34), 369 (14), 368 (60), 356

(60). HRMS [M$^+$] calcd for C$_{23}$H$_{17}$NO$_5$ 387.1107, found 387.1115.

4-Acetyl-2-formylpyrrole-1-carboxylic acid methyl ester (33)
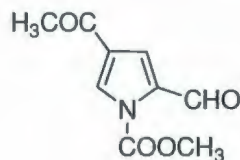
To a clear, pale yellow solution of 4-acetylpyrrole-2-carboxaldehyde (0.685 g, 5.00 mmol) in THF at 0 °C, sodium hydride (60% dispersion in mineral oil, 0.200 g, 5.00 mmol) was added. To the resulting cloudy solution, methyl chloroformate (0.390 mL, 5.00 mmol) was added after 5 min and the reaction mixture was allowed to stir for 18 h. A few drops of methanol were added to the reaction mixture and the solvent was removed under reduced pressure. Water was added to the resulting gummy mass. It was extracted with dichloromethane (3 × 25 mL). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated and recrystallized to afford **33** as a pale yellow solid (0.448 g, 46%). The filtrate was concentrated to dryness and purified by flash chromatography to afford **33** as a pale yellow solid (0.324 g, 33%). Combined yield = 0.772 g, 79%.

mp = 114-115 °C (ethyl acetate/hexane); δ_H(CDCl$_3$) = 10.35 (s, 1H, *CHO*), 8.05 (d, *J* = 1.9 Hz, 1H, H-3), 7.52 (d, *J* = 1.3 Hz, 1H, H-5), 4.12 (s, 3H, COO*CH$_3$*), 2.47 (s, 3H, CO*CH$_3$*), δ_C(CDCl$_3$) = 192.6 (*CHO*), 182.1 (CO*CH$_3$*), 150.2, 135.4, 129.4 (C-3), 127.6, 119.5 (C-5), 55.7 (COO*CH$_3$*), 27.3 (CO*CH$_3$*) ppm; Elemental analysis calcd for C$_9$H$_9$NO$_4$ C 55.39%; H 4.65%; N 7.18%, found C 55.43%; H 4.67%; N 7.05%.

(3a*S**, 4*R**, 11c*S**)-4-Acetyl-2-(6-oxo-3,3a,4,5,6,11c-hexahydro-2H-1,7-dioxa-5-aza-cyclopenta[*c*]phenanthren-4-yl)-pyrrole-1-carboxylic acid methyl ester (34b)
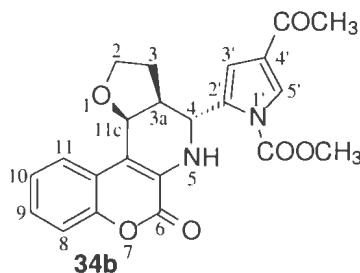
Following general experimental procedure B, 3-aminocoumarin (**17**) (0.32 g, 2.0 mmol), aldehyde **33** (0.41 g, 2.1 mmol) and DHF (0.45 mL, 6.0 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.062 g, 5.0 mol%) in acetonitrile (20 mL) at room temperature for 30 sec. The clear pale yellow solution turned into a clear orange solution over the course of the reaction. An orange residue was obtained and the *dr* was determined to be 44:56 in favor of the *exo* isomer by ^{1}H NMR analysis of the crude reaction mixture. The residue was then subjected to flash chromatography (0-10% ethyl acetate/dichloromethane) to afford **34ab** as a diastereomeric mixture (40:60 ratio 0.48 g, 59%). *Exo* isomer could be recrystallized as an off-white solid (0.15 g, 18%). *Endo* isomer could not be isolated in pure form.

34b: mp = 267-269 °C (chloroform/hexane); δ_H(CDCl$_3$) = 7.90 (d, *J* = 1.8 Hz, 1H, H-3'), 7.77-7.75 (m, 1H), 7.30-7.27 (m, 3H), 6.73 (d, *J* = 1.2 Hz, 1H, H-5'), 5.55 (s, 1H, H-5), 4.96 (d, *J* = 6.1 Hz, 1H, H-11c), 4.66 (d, *J* = 9.5 Hz, 1H, H-4), 4.05 (s, 3H, COO*CH₃*), 4.03-3.98 (m, 1H, H-2), 3.92 (dd, *J* = 15.5, 8.5 Hz, 1H, H-2), 2.90-2.86 (m, 1H, H-3a),

2.46 (s, 3H, COCH_3), 2.38-2.33 (m, 1H, H-3), 1.96-1.91 (m, 1H, H-3) ppm; δ_C(CDCl$_3$) = 193.0 (*C*OCH$_3$), 158.8 (C-6), 150.7 (*C*OOCH$_3$), 148.6, 135.8, 129.5, 127.2, 127.0 (C-3'), 126.9, 125.0, 123.5, 120.8, 116.5, 116.2, 111.9 (C-5'), 72.0 (C-11c), 66.2 (C-2), 55.3 (COO*C*H$_3$), 49.5 (C-4), 40.7 (C-3a), 30.1 (C-3), 27.3 (CO*C*H$_3$) ppm; IR ν = 3395 (m), 3139 (m), 1762 (s), 1715 (s), 1673 (s), 1631 (m), 1604 (w), 1582 (w), 1526 (w), 1504 (m), 1474 (w), 1445 (m), 1408 (w), 1396 (w), 1376 (m), 1348 (m), 1339 (m), 1324 (w), 1306 (m), 1285 (w), 1264 (s), 1240 (s), 1213 (m), 1186 (m), 1123 (w), 1170 (m), 1149 (m), 1122 (w), 1103 (s), 1072 (w), 1037 (m), 1005 (m) cm^{-1}; MS *m/z* (relative intensity) = 409 (M$^+$+1, 100), 347 (19), 331 (30), 329 (24). HRMS [M$^+$] calcd for C$_{22}$H$_{20}$N$_2$O$_6$ 408.1321, found 408.1320.

(3aS*, 4S*, 11cS*)-4-(4-Acetoxyphenyl)-2,3,3a,4,5,11c-hexahydro-2H-1,7-dioxa-6-aza-6H-furano[4,5-c]phenanthren-6-one (35a) and (3aS*, 4R*, 11cS*)-4-(4-acetoxyphenyl)-2,3,3a,4,5,11c-hexahydro-2H-1,7-dioxa-6-aza-6H-furano[4,5-c]phenanthren-6-one (35b)
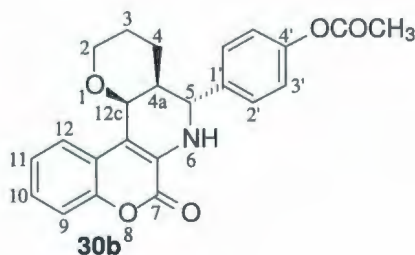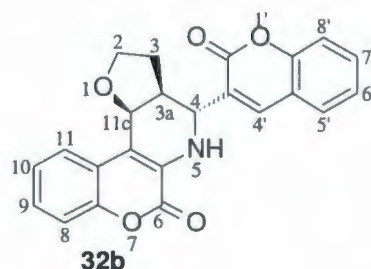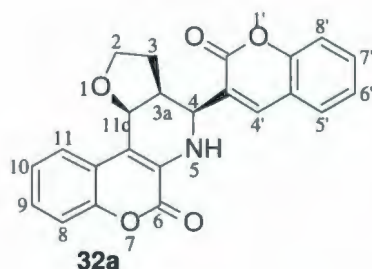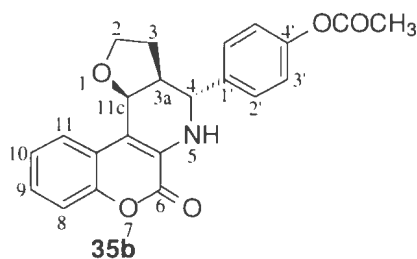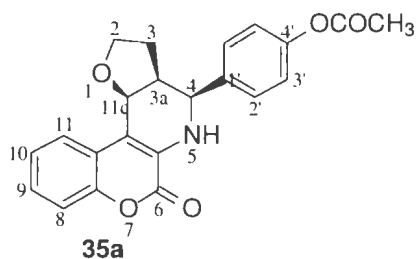
Following general experimental procedure B, 3-aminocoumarin (**17**) (2.58 g, 16.0 mmol), 4-acetoxybenzaldehyde (**29**) (2.76 g, 16.8 mmol) and DHF (3.63 mL, 48.0 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.497 g, 5.0 mol%) in acetonitrile (50 mL) at room temperature for 5 min. The reaction mixture remained a clear red solution (after the addition of dienophile) over the course of the reaction. The solvent was removed under reduced pressure to afford a yellow residue and the *dr* was determined to be 46:54 in favor of the *exo* isomer. The residue was then subjected to flash chromatography (dichloromethane) to afford **35a** as a white solid (0.45 g, 7%), **35b** as a white solid (0.67 g, 11%) and a mixed fraction (0.88 g, 15%). Combined yield = 1.99 g, 33%.

35a: mp = 183-184 °C (chloroform/hexane). δ_H(CDCl$_3$) = 7.83-7.81 (m, 1H, H-11), 7.52-7.50 (m, 2H, H-2'), 7.33-7.27 (m, 3H), 7.16-7.14 (m, 2H, H-3'), 5.49 (d, 2H, J = 7.4 Hz, H-11c), 4.94 (s, 1H, H-5), 4.72 (d, 1H, J = 2.8 Hz, H-4), 3.91 (td, 1H, J = 8.6, 2.7 Hz, H-2α), 3.81-3.76 (m, 1H, H-2β), 2.95-2.92 (m, 1H, H-3a), 2.33 (s, 3H, OCOC*H$_3$*), 2.23-2.16 (m, 1H, H-3α), 1.68-1.62 (m 1H, H-3β) ppm; δ_C(CDCl$_3$) = 169.0 (O*C*OCH$_3$), 158.9 (C-6), 150.6, 148.9, 138.1, 129.8, 127.8 (C-2'), 127.1, 124.8, 124.5 (C-11), 122.2 (C-3'), 120.3, 118.8, 116.6, 73.0 (C-11c), 67.7 (C-2), 57.6 (C-4), 47.0 (C-3a), 25.9 (C-3), 22.1 (OCO*C*H$_3$) ppm; IR ν = 3371 (w), 2869 (w), 1709 (s), 1631 (w), 1502 (m), 1204 (s), 1186 (vs), 1050 (m), 778 (s) cm^{-1}. HRMS *m/z* [M$^+$] calcd for C$_{22}$H$_{19}$NO$_5$ 377.1263, found 377.1258. **35b:** mp = 158-159 °C (chloroform/hexane). δ_H(CDCl$_3$) = 7.78-7.75 (m, 1H, H-11), 7.46 (d, 2H, J = 9.1 Hz, H-2'), 7.32-7.30 (m, 3H), 7.16 (m, 2H, J = 8.3, H-3'), 5.25 (s, 1H, H-5), 4.75 (d, 1H, J = 5.1 Hz, H-11c), 4.10 (td, 1H, J = 8.2, 6.4 Hz, H-2β), 3.97 (td, 1H, J = 9.0, 5.4 Hz, H-2α), 3.84 (d, 1H, J = 11.1 Hz, H-4), 2.52-2.47 (m, 1H, H-3a),

2.31 (s, 3H, OCOCH_3) 2.18-2.12 (m, 1H, H-3β), 1.84-1.78 (m, 1H, H-3α) ppm;

δ_C(CDCl$_3$) = 169.6 (OCOCH$_3$), 158.8 (C-6), 151.0, 148.4, 137.6, 130.8, 129.5 (C-2'),

126.8, 12.51, 123.2 (C-11), 122.3 (C-3'), 121.2, 116.6, 116.0, 72.9 (C-11c), 65.9 (C-2),

57.1 (C-4), 43.1 (C-3a), 28.6 (C-3), 21.3 (OCOCH_3) ppm; IR ν = 3305 (m), 1744 (s),

1730 (s), 105 (m), 1242 (s), 1176 (s), 1046 (m), 787 (s) cm^{-1}. HRMS *m/z* [M$^+$] calcd for

C$_{22}$H$_{19}$NO$_5$ 377.1263, found 377.1254.

(3a*S**, 4*S**, 11c*S**)-4-(10-Methoxy-6-oxo-3,3a,4,5,6,11c-hexahydro-2*H*-1,7-dioxa-5-aza-cyclopenta[*c*]phenanthren-4-yl)-benzoic acid methyl ester (36a) and (3a*S**, 4*R**, 11c*S**)-4-(10-Methoxy-6-oxo-3,3a,4,5,6,11c-hexahydro-2*H*-1,7-dioxa-5-aza-cyclopenta[*c*]phenanthren-4-yl)-benzoic acid methyl ester (36b)
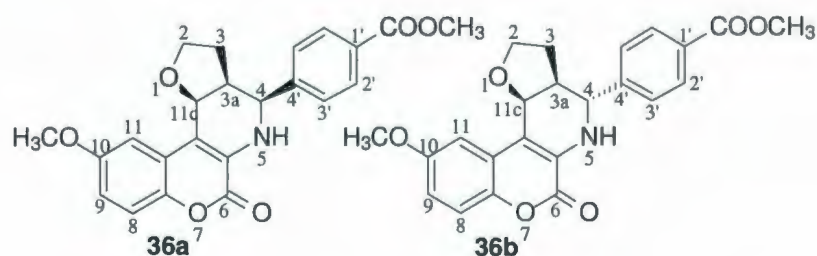
Following general experimental procedure B, 3-amino-6-methoxycoumarin (0.19

g, 1.0 mmol), 4-formyl methylbenzoate (0.17 g, 1.05 mmol) and DHF (0.23 mL, 3.0

mmol) were reacted in the presence of Yb(OTf)$_3$ (0.031 g, 5.0 mol%) in acetonitrile (30

mL) at room temperature for 20 min. The reaction mixture turned from a thick yellow

suspension to a pale yellow suspension over the course of the reaction. The solvent was

removed under reduced pressure to afford a yellow residue and the *dr* was determined to be 39:61 in favor of the *exo* isomer. The residue was then subjected to flash chromatography (dichloromethane) to afford **36a** as a white solid (0.04 g, 10%), **36b** as a white solid (0.06 g, 15%) and a mixed fraction (0.04 g, 10%). Combined yield = 0.14 g, 34%.

36a mp = 209- 210 °C (dichloromethane/hexane); δ_H(CDCl$_3$) = 8.08 (d, J = 8.6 Hz, 2H, H-2′), 7.56 (d, J = 8.1 Hz, 2H, H-3′), 7.30 (d, J = 3.2 Hz, 1H, H-11), 7.22 (d, J = 9.0 Hz, 1H, H-8), 6.90 (dd, J = 9.0, 3.2 Hz, 1H, H-9), 5.45 (d, J = 8.0 Hz, 1H, H-11c), 5.00 (s, 1H, H-5), 4.77 (d, J = 2.6 Hz, 1H, H-4), 3.94 (s, 3H, COO*CH$_3$*), 3.91-3.88 (m, 1H, H-2), 3.87 (s, 3H, C-10-*OCH$_3$*), 3.80-3.75 (m, 1H, H-2), 2.97-2.92 (m, 1H, H-3a), 2.21-2.12 (m, 1H, H-3), 1.58-1.52 (m, 1H, H-3); δ_C(CDCl$_3$) = 166.8 (C-6), 158.9, 156.6, 145.6, 143.3, 130.3 (C-2′), 130.2, 129.9, 126.7 (C-3′), 120.9, 118.6, 117.4 (C-8), 114.4 (C-9), 107.6 (C-11), 73.0 (C-11c), 67.6 (C-2), 57.0 (C-4), 56.0 (C-10-*OCH$_3$*), 52.4 (COO*CH$_3$*), 46.0 (C-3a), 25.2 (C-3) ppm; IR ν = 3364 (w), 1700 (s), 1631 (w), 1608 (w), 1579 (w), 1506 (s), 1464 (m), 1425 (m), 1365 (w), 1310 (w), 1286 (s), 1222 (m), 1197 (s), 1176 (s), 1119 (m), 1108 (m), 1086 (s), 1060 (s), 1035 (s), 1015 (m) cm^{-1}; MS (APCI) *m/z* (relative intensity) = 408 (M$^+$+1, 8), 388 (100), 376 (75) . HRMS [M$^+$] calcd for C$_{23}$H$_{21}$NO$_6$ 407.1369, found 407.1363. **36b:** mp = 168-171 °C (dichloromethane/hexane); δ_H(CDCl$_3$) = 8.09 (d, J = 8.3 Hz, 2H, H-2′), 7.52 (d, J = 8.1 Hz, H-3′), 7.24-7.22 (m, 2H), 6.88 (dd, J = 9.0, 3.0 Hz, 1H, H-9), 5.29 (s, 1H, H-5), 4.70 (d, J = 5.2 Hz, 1H, H-11c), 4.10 (td, J = 8.2, 6.7 Hz, 1H, H-2), 3.98-3.93 (m, 1H, H-2), 3.95 (s, 3H, COO*CH$_3$*), 3.87 (s, 3H, C-10-*OCH$_3$*), 3.86 (d, J = 10.4 Hz, 1H, H-4), 2.52-2.48 (m, 1H, H-3a), 2.13-2.09 (m, 1H, H-3),

1.80-1.76 (m, 1H, H-3) ppm; δ_C(CDCl$_3$) = 166.8 (C-6), 158.9, 156.9, 145.1, 143.0, 131.0, 130.8, 130.4, 128.5, 121.8, 117.5, 116.1, 113.8 (C-9), 106.7, 72.9 (C-11c), 65.8 (C-2), 57.4 (C-4), 56.1 (C-10-OCH_3), 52.5 (COOCH_3), 43.1 (C-3a), 28.4 (C-3) ppm; IR ν = 3288 (w), 1714 (s), 1633 (w), 1611 (w), 1576 (w), 1510 (m), 1435 (m), 1384 (w), 1341 (w), 1279 (s), 1219 (w), 1176 (s), 1144 (w), 1108 (m), 1068 (m), 1042 (s), 1018 (m) cm^{-1}; MS (APCI) m/z (relative intensity) = 408 (M$^+$+1, 22), 406 (32), 389 (14), 388 (55), 377 (28), 376 (100), 214 (26). HRMS [M$^+$] calcd for C$_{23}$H$_{21}$NO$_6$ 407.1369, found 407.1364.

(3aS*, 4S*, 11cS*)-4-(8-Methoxy-6-oxo-3,3a,4,5,6,11c-hexahydro-2H-1,7-dioxa-5-aza-cyclopenta[c]phenanthren-4-yl)-benzoic acid methyl ester (37a) and (3aS*, 4R*, 11cS*)-4-(8-Methoxy-6-oxo-3,3a,4,5,6,11c-hexahydro-2H-1,7-dioxa-5-aza-cyclopenta[c]phenanthren-4-yl)-benzoic acid methyl ester (37b)

Following general experimental procedure B, 3-amino-8-methoxycoumarin (0.34 g, 1.8 mmol), 4-formyl methylbenzoate (0.31 g, 1.89 mmol) and DHF (0.41 mL, 5.4 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.056 g, 5.0 mol%) in acetonitrile (18 mL) at room temperature for 10 min. The reaction mixture turned from an orange

precipitate to a clear orange solution over the course of the reaction. The solvent was removed under reduced pressure to afford a yellow residue and the *dr* was determined to be 36:64 in favor of the *exo* isomer. The residue was then subjected to flash chromatography (dichloromethane) to afford **37a** as a white solid (0.05 g, 6%), **37b** as a white solid (0.11 g, 16%) and a mixed fraction (0.09 g, 12%). Combined yield = 0.25 g, 34%.

37a: mp = 210-211 °C (dichloromethane/hexane); δ_H(CDCl$_3$) = 8.08 (d, J = 8.5 Hz, 2H, H-2'), 7.56 (d, J = 8.1 Hz, 2H, H-3'), 7.41 (d, J = 8.0 Hz, 1H, H-11), 7.20 (t, J = 8.2 Hz, 1H, H-10), 6.92 (d, J = 7.9 Hz, 1H, H-9), 5.48 (d, J = 8.1 Hz, 1H, H-11c), 5.00 (s, 1H, H-5), 4.78 (d, J = 2.9 Hz, 1H, H-4), 3.96 (s, 3H, C-8-OCH_3), 3.94 (s, 3H, COOCH_3), 3.89 (td, J = 8.5, 2.6 Hz, 1H, H-2), 3.79-3.74 (m, 1H, H-2), 2.96-2.94 (m, 1H, H-3a), 2.20-2.15 (m, 1H, H-3), 1.57-1.52 (m, 1H, H-3) ppm; δ_C(CDCl$_3$) = 166.9 (COOCH$_3$), 158.4 (C-6), 147.4 (C-8), 145.6 (C-4'), 138.5 (C-7a), 130.4 (C-2'), 130.2, 130.0, 126.6 (C-3'), 124.7 (C-10), 121.1, 119.0, 116.2 (C-11), 109.7 (C-9), 73.1 (C-11c), 67.6 (C-2), 57.1 (C-4), 56.4 (C-8-OCH_3), 52.4 (COOCH_3), 46.0 (C-3a), 25.2 (C-3) ppm; IR ν = 3361 (w), 1711 (s), 1632 (w), 1605 (m), 1579 (m), 1500 (m), 1479 (w), 1450 (m), 1344 (w), 1319 (w), 1293 (s), 1276 (m), 1201 (m), 1170 (s), 1053 (m), 1017 (m) cm^{-1}; MS (APCI) m/z (relative intensity) = 409 (M$^+$+2, 27), 408 (M$^+$+1, 100), 406 (13). HRMS [M$^+$] calcd for C$_{23}$H$_{21}$NO$_6$ 407.1369, found 407.1395. **37b:** mp = 191-192 °C (triturated with ethyl acetate); δ_H(CDCl$_3$) = 8.08 (d, J = 8.1 Hz, 2H, H-2'), 7.52 (d, J = 8.6 Hz, 2H, H-3'), 7.35 (m, 1H, H-11), 7.23 (t, J = 7.9 Hz, 1H, H-10), 6.90 (m, 1H, H-9), 5.29 (s, 1H, H-5), 4.72 (d, J = 5.1 Hz, 1H, H-11c), 4.10 (m, 1H, H-2), 3.96 (s, 3H, 8-OCH_3), 3.95 (s, 3H,

COOCH_3), 3.97-3.92 (m, 1H, H-2), 3.87 (d, J = 11.0 Hz, 1H, H-4), 2.52-1.47 (m, 1H, H-3a), 2.14-2.09 (m, 1H, H-3), 1.79-1.74 (m, 1H, H-3) ppm; δ_C(CDCl$_3$) = 166.9 (COOCH$_3$), 158.3 (C-6), 147.4, 145.1 (C-4'), 138.0 , 130.9, 130.7, 130.4 (C-2'), 128.5 (C-3'), 125.0 (C-10), 121.9, 116.2, 115.0 (C-11), 109.5 (C-9), 73.0 (C-11c), 65.7 (C-2), 57.3 (C-4), 56.4 (C-8 OCH_3), 52.5 (COOCH_3), 43.0 (C-3a), 28.4 (C-3) ppm; IR ν = 3366 (w), 1710 (s), 1631 (w), 1604 (w), 1576 (m), 1506 (w), 1480 (w), 1452 (w), 1437 (w), 1387 (w), 1345 (w), 1272 (m), 1231 (w), 1200 (w), 1175 (m), 1109 (m), 1092 (m), 1040 (w) cm^{-1}; MS (APCI) m/z (relative intensity) = 409 (M$^+$+2, 27), 408 (M$^+$+1, 100), 388 (17), 376 (11), 236 (5). HRMS [M$^+$] calcd for C$_{23}$H$_{21}$NO$_6$ 407.1369, found 407.1344.

Following general experimental procedure B, 3-amino-8-methoxycoumarin (0.096 g, 0.50 mmol), 4-formyl methylbenzoate (0.087 g, 0.53 mmol) and DHF (0.14 mL, 1.5 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.031 g, 10.0 mol%) in acetonitrile (5 mL) at room temperature for 10 min. The reaction mixture turned from an orange precipitate to a clear orange solution over the course of the reaction. The solvent was removed under reduced pressure to afford a yellow residue and the *dr* was determined to be 36:64 in favor of the *exo* isomer. The residue was then subjected to flash chromatography (5% ethyl acetate/dichloromethane) to afford **37a,b** as a white solid (0.11 g, 54%).

(3a*S**, 4*S**, 11c*S**)-4-(10-Bromo-6-oxo-3,3a,4,5,6,11c-hexahydro-2*H*-1,7-dioxa-5-aza-cyclopenta[*c*]phenanthren-4-yl)-benzoic acid methyl ester (38a) and (3a*S**, 4*R**, 11c*S**)-4-(10-Bromo-6-oxo-3,3a,4,5,6,11c-hexahydro-2*H*-1,7-dioxa-5-aza-cyclopenta[*c*]phenanthren-4-yl)-benzoic acid methyl ester (38b)

Following general experimental procedure B, 3-amino-6-bromocoumarin (0.48 g, 2.0 mmol), 4-formyl methyl benzoate (0.35 g, 2.1 mmol) and DHF (0.46 mL, 6.0 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.062 g, 5.0 mol%) in acetonitrile: chloroform (25 mL:1.0 mL) at room temperature for 20 min. The reaction mixture turned from a thick yellow suspension to a clear yellow solution over the course of the reaction. The solvent was removed under reduced pressure to afford a yellow residue and the *dr* was determined to be 44:56 in favor of the *exo* isomer. The residue was then subjected to flash chromatography (0-2% ethyl acetate/dichloromethane) to afford **38a** as a white solid (0.05 g, 6%), **38b** as a white solid (0.12 g, 13%) and a mixed fraction (0.10 g, 11%). Combined yield = 0.27 g, 30%.

38a: mp = 244-245 °C (dichloromethane/hexane); δ_H(CDCl$_3$) = 8.09 (br s, 2H, H-2'), 7.96 (s, 1H, H-11), 7.56 (br s, 2H, H-3'), 7.40 (d, *J* = 7.4 Hz, 1H, H-9), 7.16 (d, *J* = 7.8

Hz, 1H, H-8), 5.40 (d, J = 6.1 Hz, 1H, H-11c), 5.06 (br s, 1H, H-5), 4.79 (br s, 1H, H-4), 3.94 (s, 3H, COOCH_3), 3.89-3.88 (m, 1H, H-2), 3.79-3.77 (m, 1H, H-2), 2.95-2.88 (m, 1H, H-3a), 2.15-2.11 (m, 1H, H-3), 1.56 (br s, 1H, H-3) ppm; δ_C(CDCl$_3$) = 166.8 (COOCH$_3$), 158.3 (C-6), 147.6, 145.3, 130.4 (C-3′), 130.1, 129.8 (C-6), 127.1 (C-11), 126.6 (C-2′), 122.1 (C-11a), 118.1 (C-8), 117.9, 117.4, 72.7 (C-11c), 67.6 (C-2), 56.9 (C-4), 52.4 (COOCH_3), 45.9 (C-3a), 25.2 (C-3) ppm; HRMS [M$^+$] calcd for $C_{22}H_{18}BrNO_5$ 456.0368, found 456.0163. **38b:** mp = 216-217 °C (dichloromethane/hexane); δ_H(CDCl$_3$) = 8.09 (d, J = 8.5 Hz, 2H, H-2′), 7.86 (d, J = 2.1 Hz, 1H, H-11), 7.51 (d, J = 8.4 Hz, 2H, H-3′), 7.38 (dd, J = 8.6 Hz, 2.5 Hz, 1H, H-9), 7.17 (d, J = 9.0 Hz, 1H, H-8), 5.35 (s, 1H, H-5), 4.66 (d, J = 5.1 Hz, 1H, H-11c), 4.12-4.07 (m, 1H, H-2), 3.99-3.96 (m, 1H, H-2), 3.95 (s, 3H, COOCH_3), 3.86 (d, J = 11.2 Hz, 1H, H-4), 2.52-2.47 (m, 1H, H-3a), 2.14-2.09 (m, 1H, H-3), 1.79-1.74 (m, 1H, H-3) ppm; δ_C(CDCl$_3$) = 166.8 (COOCH$_3$), 158.2 (C-6), 147.2, 144.8, 131.2, 130.9, 130.4 (C-2′), 129.6 (C-9), 128.5 (C-3′), 125.7 (C-11), 123.0, 118.2 (C-8), 114.9, 72.5 (C-11c), 65.8 (C-2), 57.4 (C-4), 52.5 (COOCH_3), 42.9 (C-3a), 28.4 (C-3) ppm. IR ν = 1369 (w), 1710 (s), 1620 (w), 1594 (w), 1499 (m), 1439 (w), 1415 (m), 1336 (w), 1312 (w), 1277 (s), 1225 (m), 1191 (m), 1136 (m), 1104 (m), 1064 (m), 1044 (m), 1021 (m) cm^{-1}; MS m/z (relative intensity) = 458 (M$^+$+1, 80) and 456 (M$^+$+1, 100), 282 (6). HRMS [M$^+$] calcd for $C_{22}H_{18}BrNO_5$ 456.0368, found 456.0430.

Following general experimental procedure B, 3-amino-6-bromocoumarin (0.12 g, 0.50 mmol), 4-formyl methyl benzoate (0.087 g, 0.53 mmol) and DHF (0.14 mL, 1.5 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.031 g, 10 mol%) in acetonitrile: chloroform (4.5 mL:0.5 mL) at room temperature for 20 min. The reaction mixture

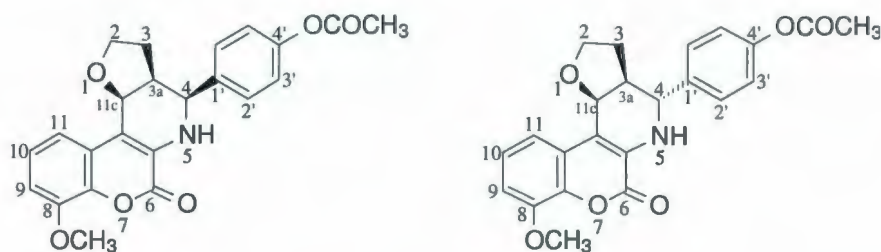turned from a thick yellow suspension to a clear yellow solution over the course of the reaction. The solvent was removed under reduced pressure to afford a yellow residue and the *dr* was determined to be 44:56 in favor of the *exo* isomer. The residue was then subjected to flash chromatography (5% ethyl acetate/dichloromethane) to afford **38a,b** as a white solid (0.043 g, 19%).

(3a*S**, 4*S**, 11c*S**)-4-(10-Nitro-6-oxo-3,3a,4,5,6,11c-hexahydro-2*H*-1,7-dioxa-5-aza-cyclopenta[*c*]phenanthren-4-yl)-benzoic acid methyl ester (39a) and (3a*S**, 4*R**, 11c*S**)-4-(10-Nitro-6-oxo-3,3a,4,5,6,11c-hexahydro-2*H*-1,7-dioxa-5-aza-cyclopenta[*c*]phenanthren-4-yl)-benzoic acid methyl ester (39b)
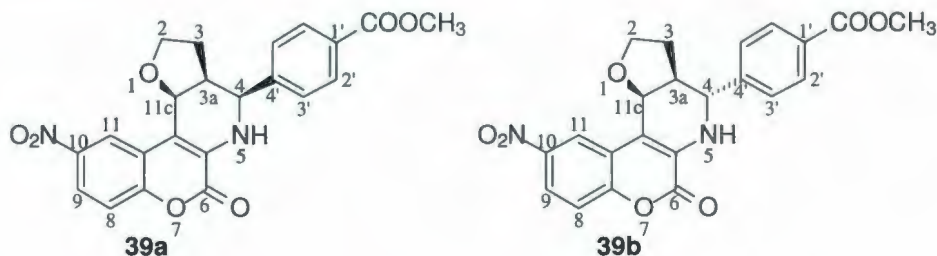
Following general experimental procedure B, 3-amino-6-nitrocoumarin (0.41 g, 2.0 mmol), 4-formyl methyl benzoate (0.35 g, 2.1 mmol) and DHF (0.46 mL, 6.0 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.062 g, 5.0 mol%) in acetonitrile (20 mL) at room tempe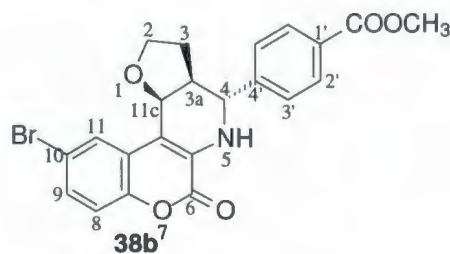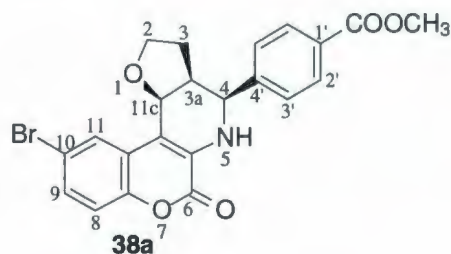rature for 20 min. The reaction mixture turned from a yellow suspension to a clear yellow solution over the course of the reaction. The solvent was removed under reduced pressure to afford a yellow residue and the *dr* was determined to be 42:58 in

favor of the *exo* isomer. The residue was then subjected to flash chromatography (0-2% ethyl acetate/dichloromethane) to afford **39a** as a yellow solid (0.05 g, 6%), **39b** as a yellow solid (0.03 g, 4%) and a mixed fraction (0.15 g, 18%). Combined yield = 0.24 g, 28%.

39a: mp = 261-262 °C (dichloromethane/hexane); δ_H(CDCl$_3$) = 8.77 (d, J = 2.7 Hz, 1H, H-11), 8.21 (dd, J = 9.0, 2.7 Hz, 1H, H-9), 8.14 (d, J = 8.4 Hz, 2H, H-2′), 7.60 (d, J = 8.5 Hz, 2H, H-3′), 7.44 (d, 9.0 Hz, 1H, H-8), 5.53 (d, J = 7.9 Hz, 1H, H-11c), 5.18 (s, 1H, H-5), 4.88 (d, J = 2.9 Hz, 1H, H-4), 3.99 (s, 3H, COOCH_3), 3.92 (td, J = 8.1, 2.5 Hz, 1H, H-2), 3.85 (td, J = 8.4, 6.5 Hz, 1H, H-2), 3.04-3.02 (m, 1H, H-3a), 2.19-2.14 (m, 1H, H-3), 1.64-1.61 (m, 1H, H-3) ppm; δ_C(CDCl$_3$) = 166.8 (COOCH$_3$), 157.8 (C-6), 152.1, 144.9, 130.52, 130.46, 126.6, 121.9, 121.0, 120.7, 117.4, 117.2, 72.3 (C-11c), 67.4 (C-2), 56.8 (C-4), 52.5 (COOCH_3), 45.8 (C-3a), 25.1 (C-3) ppm; 423 (M$^+$-1, 81), 403 (100), 391 (39), 377 (23). HRMS [M$^+$] calcd for C$_{22}$H$_{18}$N$_2$O$_7$ 422.1114, found 422.1095. **39b:** mp = 226-227 °C (dichloromethane/hexane); δ_H(CDCl$_3$) = 8.62 (s, 1H, H-11), 8.15-8.10 (m, 3H, H-8 and H-2′), 7.52 (d, J = 7.5 Hz, 2H, H-3′), 7.42 (t, J = 7.8 Hz, 1H, H-9), 5.43 (s, 1H, H-5), 4.75 (d, J = 5.1 Hz, 1H, H-11c), 4.13-4.09 (m, 1H, H-2), 4.04-3.99 (m, 1H, H-2), 3.95 (s, 3H, COOCH_3), 3.91 (d, J = 10.5 Hz, 1H, H-4), 2.55-2.54 (m, 1H, H-3a), 2.19-2.12 (m, 1H, H-3), 1.81-1.78 (m, 1H, H-3) ppm; δ_C(CDCl$_3$) = 166.7 (COOCH$_3$), 157.5 (C-6), 151.6, 145.2, 144.4 (C-4′), 131.7, 131.1 (C-5a), 130.5 (C-2′), 128.4 (C-3′), 122.0, 121.6 (C-8), 119.3 (C-11), 117.5 (C-9), 114.7, 72.4 (C-11c), 65.9 (C-2), 57.4 (C-4), 52.5 (COOCH_3), 42.9 (C-3a), 28.4 (C-3) ppm; IR ν = 3341 (w), 1712 (s), 1632 (w), 1576 (w), 1517 (m), 1435 (w), 1417 (w), 1332 (m), 1277 (s), 1247 (w), 1184 (m), 1104 (m), 1044

(m), 1020 (w) cm^{-1}; MS (APCI) *m/z* (relative intensity) = 423 (13, M$^+$+1), 421 (17), 419 (29), 404 (25), 403 (100), 391 (38), 377 (10). HRMS [M$^+$] calcd for C$_{22}$H$_{18}$N$_2$O$_7$ 422.1114, found 422.1128.

Following general experimental procedure B, 3-amino-6-nitrocoumarin (0.10 g, 0.50 mmol), 4-formyl methyl benzoate (0.087 g, 0.53 mmol) and DHF (0.14 mL, 1.5 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.031 g, 10 mol%) in acetonitrile (5 mL) at room temperature for 20 min. The reaction mixture turned from a yellow suspension to a clear yellow solution over the course of the reaction. The solvent was removed under reduced pressure to afford a yellow residue and the *dr* was determined to be 44:56 in favor of the *exo* isomer. The residue was then subjected to flash chromatography (10% ethyl acetate/hexanes) to afford **39a,b** as a yellow solid (0.040 g, 19%).

(3a*S**, 4*S**, 11c*S**)-Acetic acid 4-(8-methoxy-6-oxo-3,3a,4,5,6,11c-hexahydro-2H-1,7-dioxa-5-aza-cyclopenta[*c*]phenanthren-4-yl)-phenyl ester (40a) and (3a*S**, 4*R**, 11c*S**)-Acetic acid 4-(8-methoxy-6-oxo-3,3a,4,5,6,11c-hexahydro-2H-1,7-dioxa-5-aza-cyclopenta[*c*]phenanthren-4-yl)-phenyl ester (40b)

40a **40b**
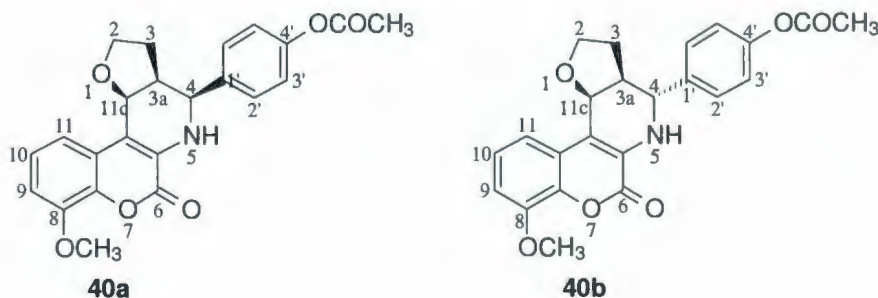
Following general experimental procedure B, 3-amino-8-methoxycoumarin (0.34 g, 1.8 mmol), 4-acetoxybenzaldehyde (0.31 g, 1.89 mmol) and DHF (0.41 mL, 5.4 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.056 g, 5.0 mol%) in acetonitrile (18 mL) at room temperature for 10 min. The reaction mixture remained a clear yellow solution over the course of the reaction. The solvent was removed under reduced pressure to afford a yellow residue and the *dr* was determined to be 38:62 in favor of the *exo* isomer. The residue was then subjected to flash chromatography (0-2% ethyl acetate/dichloromethane) to afford **40a** as a white solid (0.12 g, 16%), **40b** as a white solid (0.28 g, 16%) and a mixed fraction (0.12 g, 16%). Combined yield = 0.44 g, 60%.

40a: mp = 203-204 °C (dichloromethane/hexane); δ_H(CDCl$_3$) = 7.49 (d, *J* = 8.3 Hz, 2H, H-2′), 7.40 (dd, *J* = 8.2, 1.0 Hz, 1H, H-11), 7.22 (t, *J* = 8.0 Hz, 1H, H-10), 7.15-7.12 (m,

2H, H-3′), 6.90 (dd, J = 8.3, 1.3 Hz, 1H, H-9), 5.46 (d, J = 7.7 Hz, 1H, H-11c), 4.96 (s, 1H, H-5), 4.71 (d, J = 2.0 Hz, 1H, H-4), 3.95 (s, 3H, C-8-OCH_3), 3.89 (td, J = 8.3, 2.8 Hz, 1H, H-2), 3.79-3.74 (m, 1H, H-2), 2.92 (m, 1H, H-3a), 2.32 (s, 3H, OCOCH_3), 2.21-2.17 (m, 1H, H-3), 1.65-1.63 (m, 1H, H-3) ppm; δ_C(CDCl$_3$) = 169.6 (OCOCH$_3$), 158.4 (C-6), 150.5 (C-4′), 147.4 (C-8), 138.4 (C-7a), 138.1 (C-1′), 130.1 (C-5a), 127.7 (C-2′), 124.6 (C-10), 122.2 (C-3′), 121.2 (C-11a), 118.9 (C-11b), 116.2 (C-11), 109.6 (C-9), 73.1 (C-11c), 67.6 (C-2), 56.8 (C-4), 56.4 (C-8-OCH_3), 46.2 (C-3a), 25.3 (C-3), 21.3 (OCOCH_3) ppm; IR ν = 3374 (w), 1752 (m), 1712 (s), 1574 (m), 1495 (w), 1448 (w), 1367 (w), 1271 (w), 1193 (w), 1053 (s), 1011 (s) cm^{-1}; MS (APCI) m/z (relative intensity) = 815 (2M$^+$+1, 11), 409 (M$^+$+2, 27), 408 (M$^+$+1, 100), 406 (23), 366 (16), 334 (10). HRMS [M$^+$] calcd for C$_{23}$H$_{21}$NO$_6$ 407.1369, found 407.1347. **40b:** mp = 197-198 °C (triturated with ethyl acetate); δ_H(CDCl$_3$) = 7.45 (d, J = 9.0 Hz, 2H, H-2′), 7.34 (dd, J = 7.2, 0.9 Hz, 1H, H-11), 7.22 (t, J = 7.8 Hz, 1H, H-10), 7.14 (d, J = 9.1 Hz, 2H, H-3′), 6.88 (dd, J = 8.3, 1.0 Hz, 1H, H-9), 5.26 (s, 1H, H-5, H-5), 4.71 (d, J = 4.8 Hz, 1H, H-11c), 4.10-4.06 (td, J = 8.6, 6.6 Hz, 1H, H-2), 3.96-3.92 (m, 1H, H-2), 3.95 (s, 3H, C-8-OCH_3), 3.81 (d, J = 10.9 Hz, 1H, H-4), 2.48-2.45 (m, 1H, H-3a), 2.32 (s, 3H, OCOCH_3), 2.14-2.11 (m, 1H, H-3), 1.81-1.78 (m, 1H, H-3) ppm; δ_C(CDCl$_3$) = 169.5 (OCOCH$_3$)), 158.3 (C-6), 151.0, 147.4 (C-8), 138.0 (C-1′), 137.5, 131.0, 129.5 (C-2′), 124.9 (C-10), 122.2 (C-3′), 122.1 (C-11a), 115.9, 115.0 (C-11), 109.4 (C-9), 73.0 (C-11c), 65.7 (C-2), 57.0 (C-4), 56.4 (C-8-OCH_3), 42.9 (C-3a), 28.6 (C-3), 21.4 (OCOCH_3) ppm; IR ν = 3327 (w), 1751 (m), 1715 (m), 1653 (w), 1628 (w), 1604 (w), 1576 (m), 1503 (w), 1479 (w), 1449 (w), 1439 (m), 1365 (w), 1334 (w), 1277 (w), 1225 (s), 1201 (s), 1175 (s), 1167 (s),

1038 (m), 1017 (w) cm^{-1}; MS (APCI) m/z (relative intensity) = 815 (2M$^+$+1, 28), 409 (M$^+$+2, 27), 408 (M$^+$+1, 100), 366 (5). HRMS [M$^+$] calcd for C$_{23}$H$_{21}$NO$_6$ 407.1369, found 407.1342.

(2S*,4S*)-(2-(4-Nitrophenyl)-4-(4-phenylsulfanyl)-1,2,3,4-tetrahydro-9-oxa-1-aza-10H-phenanthren-10-one (42a) and (2R*,4S*)-(2-(4-nitrophenyl)-4-(4-phenylsulfanyl)-1,2,3,4-tetrahydro-9-oxa-1-aza-10H-phenanthren-10-one (42b)
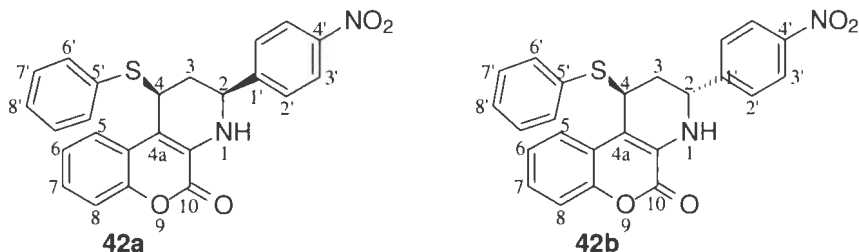
Following general experimental procedure B, 3-aminocoumarin (**5**) (1.61 g, 10.0 mmol), 4-nitrobenzaldehyde (**8**) (1.59 g, 10.5 mmol) and phenyl vinyl sulfide (3.90 mL, 30.0 mmol) were reacted in the presence of Yb(OTf)$_3$ (0.310 g, 5.00 mol%) in acetonitrile (50 mL) at room temperature for 17 h. The clear yellow solution turned into a thick yellow suspension over the course of the reaction. The resulting yellow residue was subjected to flash chromatography (5-20% ethyl acetate/hexanes) to afford **42a** as a yellow solid (1.3 g, 29%), **42b** as a yellow solid (0.082 g, 2%) and mixed fraction (0.31 g, 7%). The *dr* was determined to be 59:41 in favor of the *endo* isomer by 1H NMR analysis of the crude reaction mixture. Combined yield = 1.68 g, 38%.

42a: mp = 225-226 °C (chloroform/hexane). δ_H(CDCl$_3$) = 8.26 (d, 2H, J = 8.5 Hz, H-3'), 7.77-7.24 (m, 1H, H-5), 7.62 (d, 2H, J = 8.9 Hz, H-2'), 7.59-7.58 (m, 2H, H-6'), 7.43-7.42 (m, 2H), 7.38-7.32 (m, 4H), 5.26 (s, 1H, H-1), 5.11 (dd, 1H, J = 11.6, 3.3 Hz, H-2), 4.64 (dd, 1H, J = 3.4, 1.6 Hz, H-4), 2.34 (dt, 1H, J = 13.4, 2.0 Hz, H-3β), 2.20-2.12 (m, 1H, H-3α). δ_C(CDCl$_3$) = 158.4 (C-10), 149.2, 149.1, 148.3, 148.1, 134.1, 132.6, 129.8, 128.5, 127.9, 126.9, 125.0 (C-2'), 124.4 (C-3'), 122.2 (C-5), 119.8, 117.0, 113.6, 51.2 (C-2), 41.5 (C-4), 36.1 (C-3). IR ν = 3387 (w), 1719 (s), 1629 (m), 1599 (w), 1518 (m), 1504 (m), 1347 (m), 1328 (m), 1195 (m), 1069 (w), 782 (w), 692 (m) cm^{-1}. HRMS m/z [M$^+$] calcd for C$_{24}$H$_{18}$N$_2$O$_4$S 430.0987, found 430.1015.   **42b**: mp = 200-201 °C (chloroform/hexane). δ_H(CDCl$_3$) = 8.20 (d, 2H, J = 8.4 Hz, C-3'), 7.67 (dd, 1H, J = 7.6, 1.8 Hz, H-5), 7.48 (d, 2H, J = 9.4 Hz, H-2'), 7.37-7.27 (m, 6H), 7.16-7.08 (m, 2H), 5.59 (s, 1H, H-1), 4.92 (t, 1H, J = 4.6 Hz, H-2), 4.67 (t, 1H, J = 3.9 Hz, H-4), 2.71 (dt, 1H, J = 14.4, 3.4 Hz, H-3α), 2.60 (dt, 1H, J = 14.6, 6.2 Hz, H-3β) ppm; δ_C(CDCl$_3$) = 158.5 (C-10), 150.6, 148.1, 147.5, 134.3, 132.2, 129.4, 129.3, 128.1, 127.4, 126.8 (C-2'), 124.9, 123.9 (C-3'), 122.6 (C-5), 119.8, 116.8, 113.8, 52.2 (C-2), 40.1 (C-4), 33.4 (C-3) ppm; IR ν = 3374 (w), 1701 (s), 1623 (m), 1516 (s), 1336 (m), 1314 (w), 1212 (m), 1073 (m), 850 (m), 741 (s), 694 (m) cm^{-1}. HRMS m/z [M$^+$] calcd for C$_{24}$H$_{18}$N$_2$O$_4$S 430.0987, found 430.1001.

(3aS*, 4S*, 12cS*)-4-(4-Hydroxyphenyl)-2,3,3a,4,5,11c-hexahydro-1,7-dioxa-5-aza-cyclopenta[c]phenanthren-6-one (43)
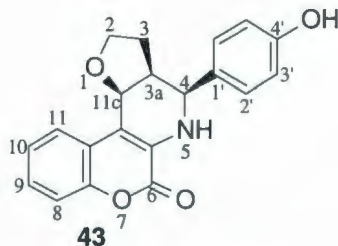
To a clear colorless solution of **35a** (38 mg, 0.10 mmol) in 1:1 methanol:chloroform (5 mL) was added K_2CO_3 (17 mg, 0.12 mmol) and the reaction mixture was stirred at room temperature for 16 h. The solvents were removed under reduced pressure and the residue obtained was dissolved in chloroform (10 mL), washed with 1.0 M HCl (5.0 mL). The two layers were separated. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the solid was recrystallized from acetone/hexanes to afford **43** as a white solid (24 mg, 72%).

mp = 221-222 °C (acetone); δ_H(CDCl$_3$) = 7.81 (d, J = 6.0 Hz, 1H), 7.43 (d, J = 8.5 Hz, 2H, H-2'), 7.30-7.27 (m, 3H), 6.87 (d, J = 8.5 Hz, 2H, H-3'), 5.47 (d, J = 8.4 Hz, 1H, H-11c), 5.08 (s, 1H, *OH*), 4.91 (s, 1H, H-5), 4.65 (d, J = 2.9 Hz, 1H, H-4), 3.90 (td, J = 8.9, 2.5 Hz, 1H, H-2), 3.81-3.74 (m, 1H, H-2), 2.93-2.88 (m, 1H, H-3a), 2.24-2.15 (m, 1H, H-3), 1.67-1.62 (m, 1H, H-3) ppm; δ_C(CDCl$_3$) = 159.1 (C-6), 155.8 (C-4'), 148.8, 133.0, 130.2, 128.3 (C-2'), 127.2, 125.1, 124.6, 120.5, 118.9, 116.8, 116.1 (C-3'), 73.3 (C-11c), 67.9 (C-2), 56.9 (C-4), 46.7 (C-3a), 25.5 (C-3) ppm; IR ν = 3287 (w), 1700 (m), 1684 (s), 1653 (s), 1616 (m), 1558 (s), 1539 (m), 1506 (s), 1217 (m), 1061 (m) cm^{-1}; MS *m/z* (relative intensity) = 336 (M$^+$+1, 32), 335 (23), 317 (19), 316 (85), 305 (22), 304 (100). HRMS [M$^+$] calcd for $C_{20}H_{17}NO_4$ 335.1158, found 335.1143.

(4a*S**, 5*R**, 12c*S**)-4-(7-Oxo-2,3,4,4a,5,6,7,12c-octahydro-1,8-dioxa-6-aza--benzo[*c*]phenanthren-5-yl)-benzoic acid (44)

44
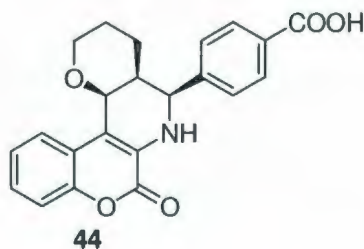
A suspension of **28b** (78 mg, 0.20 mmol) in 1M KOH/MeOH (5.0 mL) was heated at reflux for 1 h. The reaction mixture was acidified with 6 M HCl. The resulting precipitate was filtered under suction and washed with water. The product was air dried to afford **50** as a white solid (74 mg, 99%).

mp = 258-259 °C. δ_H(CDCl$_3$) = 12.84 (br s, 1H, *COOH*), 7.96 (d, *J* = 7.9 Hz, 2H, H-2'), 7.60 (d, *J* = 5.6 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 2H, H-3'), 7.30-7.27 (m, 3H), 6.27 (s, 1H, *NH*), 4.71 (s, 1H), 4.68 (d, *J* = 11.4 Hz, 1H, H-5), 3.94 (d, *J* = 9.6 Hz, 1H), 3.79-3.74 (m, 1H), 2.01-1.99 (m, 1H), 1.83-1.70 (m, 2H), 1.34-1.24 (m, 2H) ppm; δ_C(CDCl$_3$) = 167.2 (*COOH*), 157.6 (C-7), 147.4, 146.4, 130.2, 130.0, 129.4, 128.1, 125.7, 124.6, 122.1, 120.4, 115.8, 113.8, 68.5 (C-11c), 67.8 (C-2), 53.5 (C-5), 37.3 (C-4a), 22.9 (C-3), 21.4 (C-4) ppm; IR ν = 3315 (m), 1700 (s), 1680 (s), 1625 (m), 1575 (w), 1516 (m), 1484 (w), 1454 (w), 1419 (m), 1364 (w), 1329 (w), 1284 (w), 1264 (m), 1225 (s), 1195 (s), 1185 (s), 1133 (s), 1109 (w), 1091 (m), 1060 (m), 1018 (s) cm^{-1}; MS (ESI) *m/z* (relative

intensity) = 376 (M$^+$-1, 100). Elemental analysis calcd for C$_{22}$H$_{19}$NO$_5$; C 70.02%; H 5.07%; N 3.71%, found C 68.89; H 5.00%; N 3.63%.

4-[3-(3-Hydroxypropyl)-10-oxo-10H-9-oxa-1-aza-phenanthren-2-yl]-benzoic acid methyl ester (45) and 4-[3-(3-Formyloxypropyl)-10-oxo-10H-9-oxa-1-aza-phenanthren-2-yl]-benzoic acid methyl ester (46)
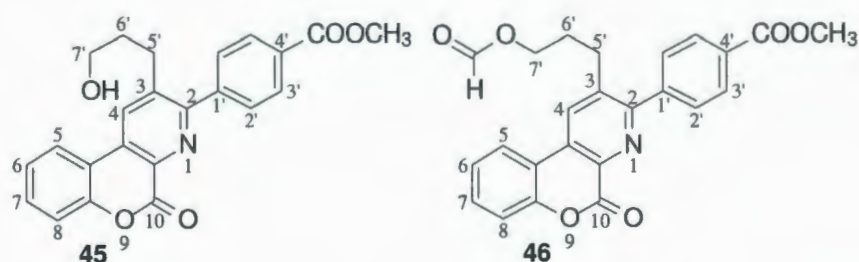
Method 1: To a clear colorless solution of **28b** (78 mg, 0.20 mmol) in DMF (3.0 mL), was added TMSCl (0.04 mL, 0.30 mmol), followed by the addition of sodium iodide (45 mg, 0.30 mmol). The resulting mixture was heated at 50 °C for 18 h and then at 90 °C for 150 h. The reaction mixture was allowed to cool to room temperature. Ice cold water (15.0 mL) was added to it and the resulting white suspension was allowed to stir at room temperature for 1 h. It was extracted with ethyl acetate (20 mL). The aqueous layer was saturated with NaCl and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography

(30-100% ethyl acetate/hexanes) to afford **28b** (8.0 mg, 10%), **45** (18 mg, 23%) and **46** (25 mg, 30%).

45: mp = 224-226 °C; δ_H(DMSO-d$_6$) = 8.87 (s, 1H, H-4), 8.50 (dd, J =8.4, 1.7 Hz, 1H, H-5), 8.12 (d, J = 8.2 Hz, 2H, H-3'), 7.75 (d, J = 8.2 Hz, 2H, H-2'), 7.64 (t, J = 7.4 Hz, 1H), 7.46-7.44 (m, 2H), 4.48 (t, J = 5.1 Hz, 1H, *OH*), 3.87 (s, 3H, CO*OCH$_3$*), 3.38-3.35 (m, 2H, H-7'), 2.90-2.86 (m, 2H, H-5'), 1.76-1.71 (m, 2H, H-6') ppm; δ_C(DMSO-d$_6$) = 166.0 (*CO*OCH$_3$), 159.0 (C-10), 157.9, 150.8, 143.6, 142.1, 135.2, 132.2, 130.6, 129.5, 129.3, 129.1, 124.8, 124.7, 124.5, 117.2, 116.7, 60.0 (C-7'), 52.3 (CO*OCH$_3$*), 32.9 (C-5'), 29.1 (C-6') ppm; IR ν = 3524 (m), 1734 (m), 1708 (s), 1612 (w), 1457 (w), 1436 (m), 1274 (s), 1237 (w), 1180 (s), 1051 (w), 1020 (w) cm^{-1}; MS (APCI) *m/z* (relative intensity) = 391 (M$^+$+2, 100); HRMS [M$^+$] calcd for C$_{23}$H$_{19}$NO$_5$ 389.1263, found = 389.1267. **46:** mp = 166-167 °C; δ_H(CDCl$_3$) = 8.40 (s, 1H, H-4), 8.16 (d, J =8.1 Hz, 2H, H-3'), 8.09 (d, J = 7.7 Hz, 1H, H-5), 7.99 (s, 1H, *CHO*), 7.64 (d, J = 8.0 Hz, 2H, H-2'), 7.77 (t, J = 7.7 Hz, 1H, H-6), 7.43-7.40 (m, 2H), 4.13 (t, J = 6.2 Hz, 2H, H-7'), 3.97 (s, 3H, *COOCH$_3$*), 2.97 (t, J = 7.8 Hz, 2H, H-5'), 1.98-1.92 (m, 2H, H-6'), ppm; δ_C(CDCl$_3$) = 166.8 (*CO*OCH$_3$), 160.9 (*CHO*), 160.5 (C-10), 158.9, 151.5, 143.3, 140.9, 136.2, 131.7, 131.3, 131.0, 130.7, 130.0, 129.3, 125.1, 123.3, 118.2, 116.7, 62.8 (C-7'), 52.5 (CO*OCH$_3$*), 29.8 (C-6'), 20.9 (C-6') ppm; IR ν= 3418 (s), 1748 (m), 1719 (s), 1700 (s), 1638 (s), 1617 (s),. 1558 (w), 1508 (w), 1458 (w), 1434 (w), 1385 (m), 1283 (m), 1169 (m), 1115 (w) cm^{-1}; MS (APCI) *m/z* (relative intensity) = 419 (M$^+$+2, 29), 418 (M$^+$+1, 100); HRMS [M$^+$] calcd for C$_{24}$H$_{19}$NO$_6$ 417.1212, found 417.1210.

Method 2: To a clear colorless solution of **28a,b** (~1:1 mixture of *endo* and *exo* diastereomers, 0.20 g, 0.50 mmol) in dichloromethane (15 mL) at room temperature in the dark was added a 1.0 M solution of Br_2 in dichloromethane (1.05 mmol) dropwise over 2 min. After the addition, the solution turned yellow-turbid. The reaction mixture was stirred for 1 h. The reaction mixture turned into a white suspension over the course of the reaction. Solid $NaHSO_4$ was added to the reaction mixture and diluted with ethyl acetate. This solution was washed with 1.0 M Na_2CO_3 solution followed by a wash with brine. The organic layer was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the solid was recrystallized from ethyl acetate/hexane to afford **45** as a white solid (0.12 g, 61%).

6-(4-Carboxyphenyl)-2-(2-hydroxyphenyl)-5-(3-hydroxypropyl)-pyridine-2-carboxylic acid (47)

47
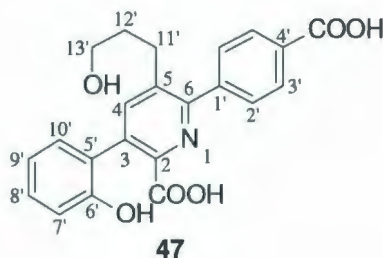
A solution of **45** (50 mg, 0.13 mmol) in 10 M KOH (3.0 mL) was stirred at room temperature for 16 h. The reaction mixture was cooled in an ice bath and 6.0 M HCl was added dropwise untill the solution became acidic (pH = 5.0). The resulting white

precipitate was filtered under suction and washed with cold water and air dried to afford **47** as a white solid (33 mg, 66%).

mp = 250-251 °C (ethanol); δ_H(CDCl$_3$) = 8.70 (s, 1H, H-4), 8.31 (d, J =7.2, 1H, H-10′), 8.19 (d, J = 8.4 Hz, 2H, H-3′), 7.74 (s, 1H, C-6′-OH), 7.68 (d, J = 7.6 Hz, 2H, H-2′), 7.63 (t, J = 7.6 Hz, 1H, H-8′), 7.49 (t, J = 7.8 Hz, 1H, H-9′), 7.44 (d, J = 8.4 Hz, 1H, H-7′), 3.53 (t, J = 6.1 Hz, 2H, H-13′), 2.98 (t, J = 8.0 Hz, 2H, H-11′), 1.82 (p, J = 6.2 Hz, 2H, H-12′) ppm; δ_C(DMSO-d$_6$) = 167.0, 159.2, 157.9, 150.8, 143.2, 142.1, 135.1, 132.1 (C-4), 131.3, 130.7, 130.5 (C-3′), 129.2 (C-2′), 124.8, 124.4 (C-10′), 117.2, 116.7, 60.1 (C-13′), 32.9 (C-12′), 29.1 (C-11′) ppm; IR ν = 3639 (br, s), 3416 (br, s), 1718 (s), 1701 (s), 1653 (w), 1636 (w), 1617 (m), 1457 (w), 1437 (m), 1384 (w), 1235 (s), 1177 (s), 1118 (w) cm^{-1}; MS (ESI) m/z (relative intensity) = 375 (M-17, 31), 374 (M-18, 100), 212 (90); Elemental analysis calcd for C$_{22}$H$_{19}$NO$_6$; C 67.17%; H 4.87%; N 3.56%, found C 67.54%; H 4.36%; N 3.54%.

Acetic acid-4-[3-(2-hydroxyethyl)-10-oxo-10*H*-9-oxa-1-aza-phenanthren-2-yl]-phenyl ester (48)
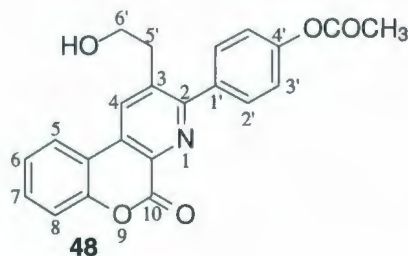
To a clear colorless solution of **35a,b** (~1:1 mixture of *endo* and *exo* diastereomers, 0.19 g, 0.50 mmol) in dichloromethane (15 mL) at room temperature in the dark was added a 1.0 M solution of Br_2 in dichloromethane (1.05 mmol) dropwise over 2 min. After the addition, the solution turned yellow-turbid. The reaction mixture was stirred for 1 h. The reaction mixture turned into a white suspension over the course of the reaction. Solid $NaHSO_4$ was added to the reaction mixture and diluted with ethyl acetate. This solution was washed with 1.0 M Na_2CO_3 solution followed by a wash with brine. The organic layer was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (20% ethyl acetate/dichloromethane) to afford **48** as a white solid (0.15 g, 80%).

mp = 208-209 °C; δ_H(DMSO-d_6) = 8.85 (s, 1H, H-4), 8.43 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H, H-3'), 7.61 (t, *J* = 7.6 Hz, 1H), 7.46-7.44 (m, 2H), 7.30 (d, *J* = 8.9 Hz, 2H, H-2'), 4.82 (t, *J* = 5.1 Hz, 1H, *OH*), 3.73 (q, *J* = 6.0, 2H, H-6'), 3.02 (t, *J* = 6.5 Hz, 2H, H-5'), 2.35 (s, 3H, OCOC*H*$_3$) ppm; δ_C(DMSO-d_6) = 169.1 (O*C*OCH$_3$), 159.7 (C-10), 158.0, 150.73, 150.66, 139.4, 136.5, 135.1, 132.5, 131.2, 130.4, 130.0, 124.8, 124.2, 121.6, 117.1, 116.7, 60.6 (C-6'), 35.6 (C-5'), 20.9 (OCOC*H*$_3$) ppm; IR *v* = 3412 (br, w), 1740

(s), 1653 (w), 1600 (w), 1460 (m), 1436 (m), 1328 (w), 1301 (m), 1216 (s), 1181 (s), 1167 (s), 1114 (m), 1096 (w), 1053 (w), 1014 (w) cm^{-1}; MS (APCI) m/z (relative intensity) = 376 (M$^+$+1, 100); HRMS [M$^+$] calcd for $C_{22}H_{17}NO_5$ = 375.1107, found = 375.1110.

3-(2-Hydroxyethyl)-2-(2-oxo-2H-chromen-3-yl)-9-oxa-1-aza-phenanthren-10-one (49)

49

To a clear pale yellow solution of **32a,b** (~1:1 mixture of *endo* and *exo* diastereomers, 0.50 g, 1.3 mmol) in dichloromethane (20 mL) at room temperature in the dark was added a 1.0 M solution of Br$_2$ in dichloromethane (2.7 mmol) dropwise over 2 min. After the addition, the solution turned yellow-turbid. The reaction mixture was stirred for 24 h. The reaction mixture remained yellow over the course of the reaction. Solid NaHSO$_4$ was added to the reaction mixture and diluted with ethyl acetate. This solution was washed with 1.0 M Na$_2$CO$_3$ solution followed by a wash with brine. The organic layer was then dried over anhydrous sodium sulfate. The solvent was removed

under reduced pressure and the residue was subjected to flash chromatography (10% ethyl acetate/dichloromethane) to afford **49** as a white solid (0.04 g, 9%).

mp = 243-244 °C; δ_H(DMSO-d_6) = 8.90 (s, 1H, H-4), 8.45 (dd, J = 9.2, 1.5 Hz, 1H), 8.34 (s, 1H), 7.90 (dd, J = 8.4, 1.6 Hz, 1H), 7.75-7.72 (m, 1H), 7.67-7.63 (m, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.50-7.44 (m, 3H), 4.73 (t, J = 5.4 Hz, 1H, *OH*), 3.72-3.68 (m, 2H, H-10′), 2.94 (t, J = 6.7 Hz, 2H, H-9′); δ_C(DMSO-d_6) = 159.3 (C-2′), 157.8 (C-10), 154.8, 153.6, 150.9, 144.2, 143.7, 135.2, 132.7, 131.5, 131.4, 129.1, 127.7, 126.8, 124.9, 124.8, 118.7, 117.2, 116.6, 116.3, 60.0 (C-11′), 32.8 (C-9′), 28.8 (C-10′) ppm; IR ν = 3402 (br, w),1717 (s), 1701 (s), 1686 (m), 1648 (s), 1635 (m), 1576 (m), 1558 (m), 1539 (m), 1507 (m), 1457 (m), 1117 (w) cm^{-1}; MS (APCI) m/z (relative intensity) = 387 (M$^+$+2, 26), 386 (M$^+$+1, 100),. HRMS [M$^+$] calcd for $C_{23}H_{15}NO_5$ 385.0950, found 385.0956.

3-(3-Hydroxypropyl)-2-(2-oxo-2*H*-chromen-3-yl)-9-oxa-1-aza-phenanthren-10-one (50)
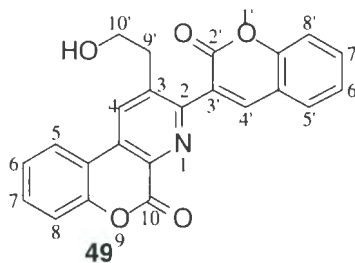

50
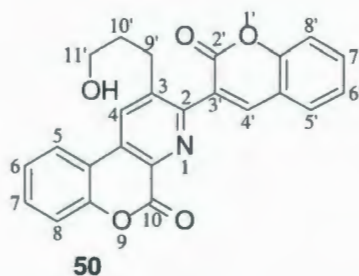
To a clear pale yellow solution of **26a,b** (~1:1 mixture of *endo* and *exo* diastereomers, 0.35 g, 0.86 mmol) in dichloromethane (30 mL) at room temperature in the dark was added a 1.0 M solution of Br$_2$ in dichloromethane (1.8 mmol) dropwise over

3 min. After the addition, the reaction mixture turned to a clear orange solution and then to an orange suspension. The reaction mixture was stirred for 22 h. Additional Br_2 in dichloromethane (0.9 mmol) was added to the reaction mixture and the reaction mixture was stirred for 4 h. Solid $NaHSO_4$ was added to the reaction mixture and diluted with ethyl acetate. This solution was washed with 1.0 M Na_2CO_3 solution followed by a wash with brine. The organic layer was then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (40% ethyl acetate/hexanes) to afford **50** as a white solid (0.13 g, 39%). mp = 256-258° C; δ_H(CDCl$_3$) = 8.43 (s, 1H, H-4), 8.12 (s, 1H), 8.10-8.08 (m, 1H), 7.64-7.55 (m, 3H), 7.44-7.40 (m, 2H), 7.36 (t, J = 7.5 Hz, 1H), 3.72 (t, J = 5.8 Hz, 2H, H-11'), 2.98 (t, J = 7.7 Hz, 2H, H-9'), 2.06-2.01 (m, 2H, H-10') ppm; δ_C(DMSO-d$_6$) = 159.3 (C-2'), 157.8 (C-10), 154.8, 153.6, 150.9, 144.2, 143.7, 135.2, 132.7, 131.5, 131.4, 129.1, 127.7, 126.8, 124.9, 124.8, 118.7, 117.2, 116.6, 116.3, 60.0 (C-11'), 32.8 (C-9'), 28.8 (C-10') ppm; IR ν = 3401 (br, w), 1734 (m), 1718 (s), 1700 (s), 1684 (s), 1651 (s), 1576 (m), 1558 (m), 1539 (m), 1507 (m), 1457 (m), 1117 (m) cm^{-1}; MS m/z (relative intensity) = 400 (M$^+$+1, 100),. HRMS [M$^+$] calcd for $C_{24}H_{17}NO_5$ 399.1107, found 399.1069.

2-(4-Nitrophenyl)-9-oxa-1-aza-phenanthren-10-one (53)

53
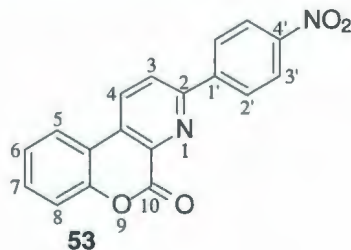
To a clear, yellow solution of **42a,b** (1.00:0.28 ratio, 120 mg, 0.278 mmol) in a 4:1 dioxan:water mixture (10 mL) was added sodium periodate (596 mg, 2.78 mmol). The reaction mixture was heated at reflux for 23 h. The reaction mixture was allowed to cool to room temperature and then saturated $NaHCO_3$ (15 mL) was added to the reaction mixture. It was extracted with ethyl acetate (3 × 20 mL). Organic layers were combined and washed with brine. The organic layer was then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was triturated with dichloromethane and air-dried to afford **53** as a brown solid (78 mg, 89%).

mp = 270-271 °C; δ_H(DMSO-d_6) = 9.03 (d, J = 9.2 Hz, 1H), 8.65 (d, J = 9.1 Hz, 1H), 8.53 (d, J = 8.8 Hz, 2H, H-3′), 8.44 (d, J = 7.5 Hz, 1H), 8.39 (d, J = 8.9 Hz, 2H), 7.63 (t, J = 8.0 Hz, 1H), 7.46-7.44 (m, 2H) ppm; δ_C(DMSO-d_6) = 158.7 (C-10), 155.5, 151.6, 149.1, 143.8, 138.7, 133.9, 132.5, 132.1, 129.0, 127.2, 125.8, 125.4, 125.0, 118.1, 117.6 ppm; MS m/z (relative intensity) = 324 (M^++2, 29), 323 (M^++1, 100). HRMS [M^++H] calcd for $C_{18}H_{11}N_2O_4$ 319.0719, found = 319.0720.

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2.6 Appendix

2.6.1 ^{1}H and ^{13}C NMR Spectra for Individual Compounds

22a

22b

24a

24b

26a

26b

28b

30b

32a

32b

H₃COC

CHO

N

COOCH₃

33

34b

35a

35b

36a

36b

37a

37b

38a

38b

39a

176

39b

40a

42a

42b

43

44

45

46

47

48

50

1,4-dioxan

53

1,4-dioxan
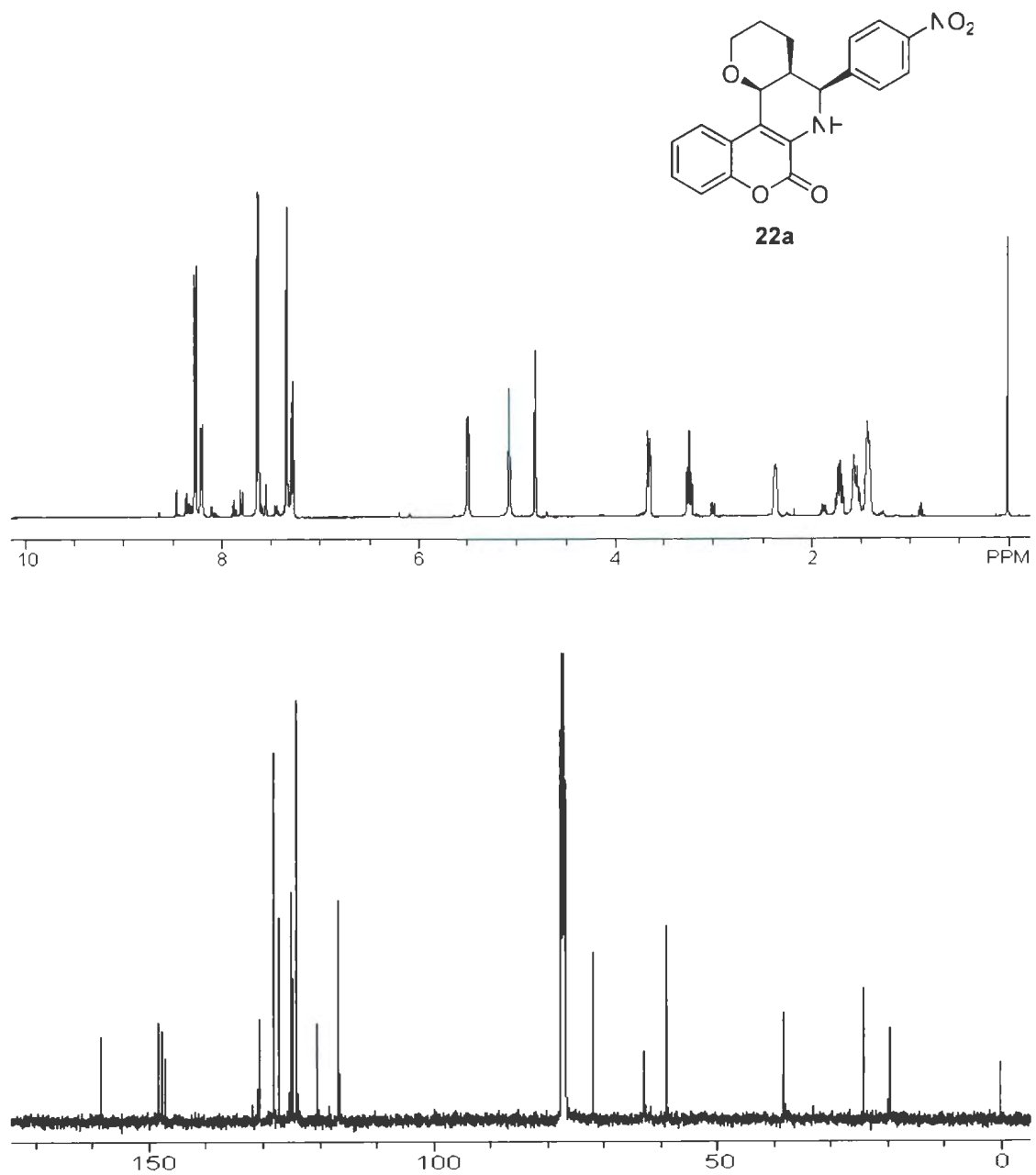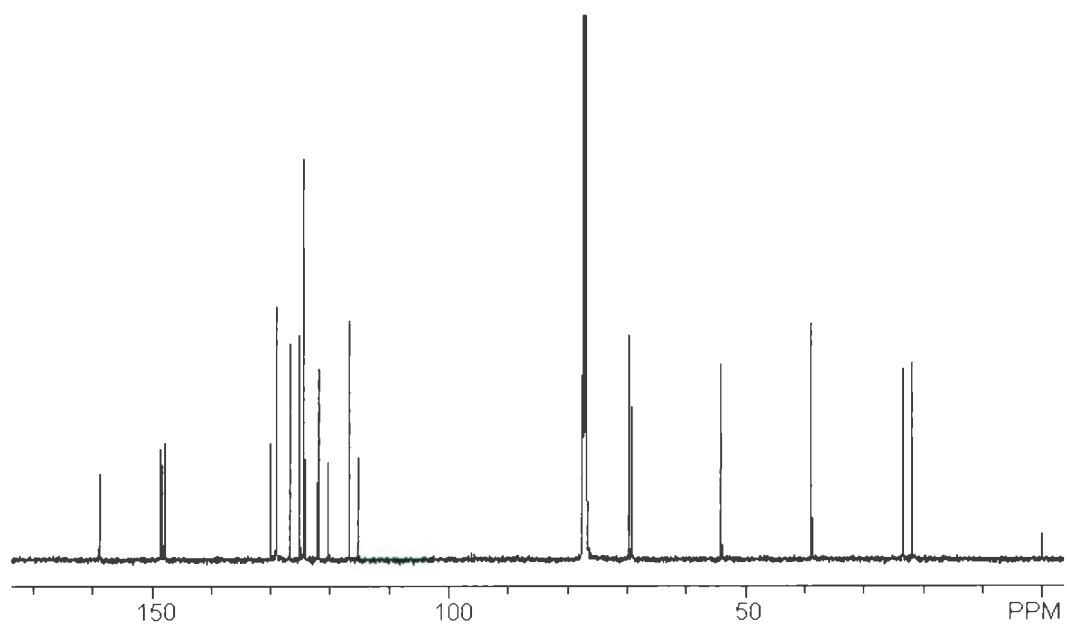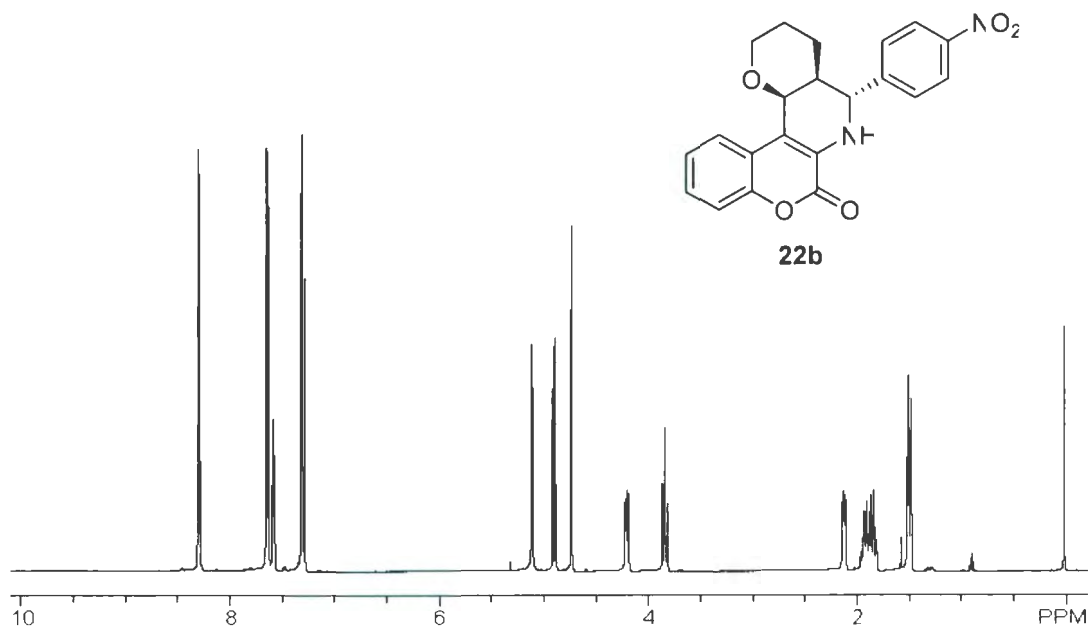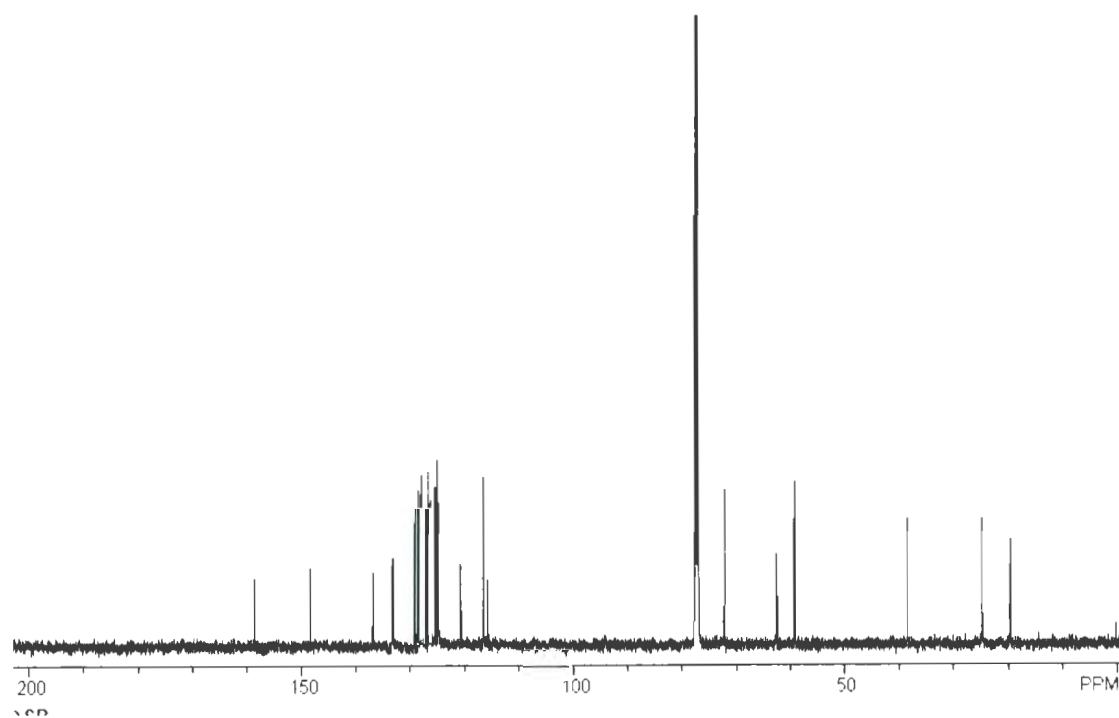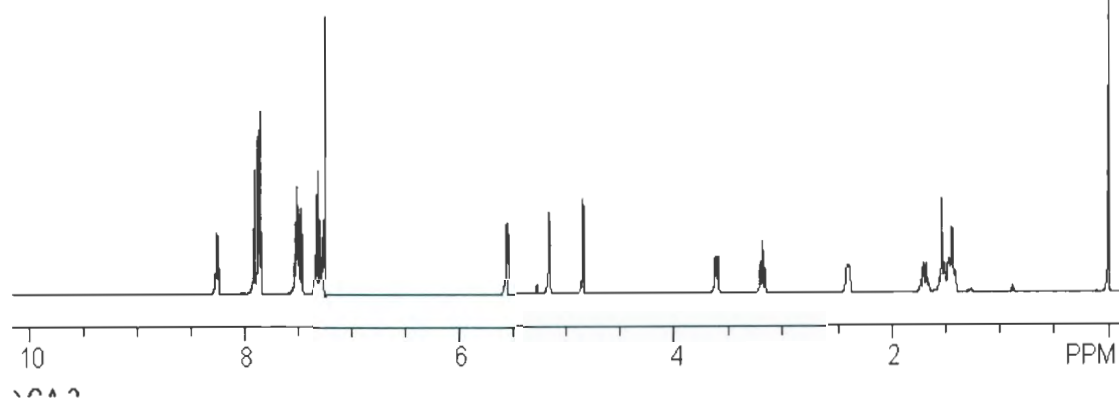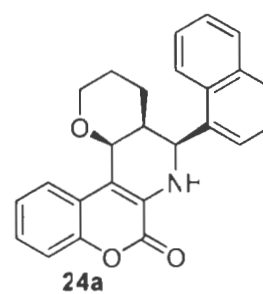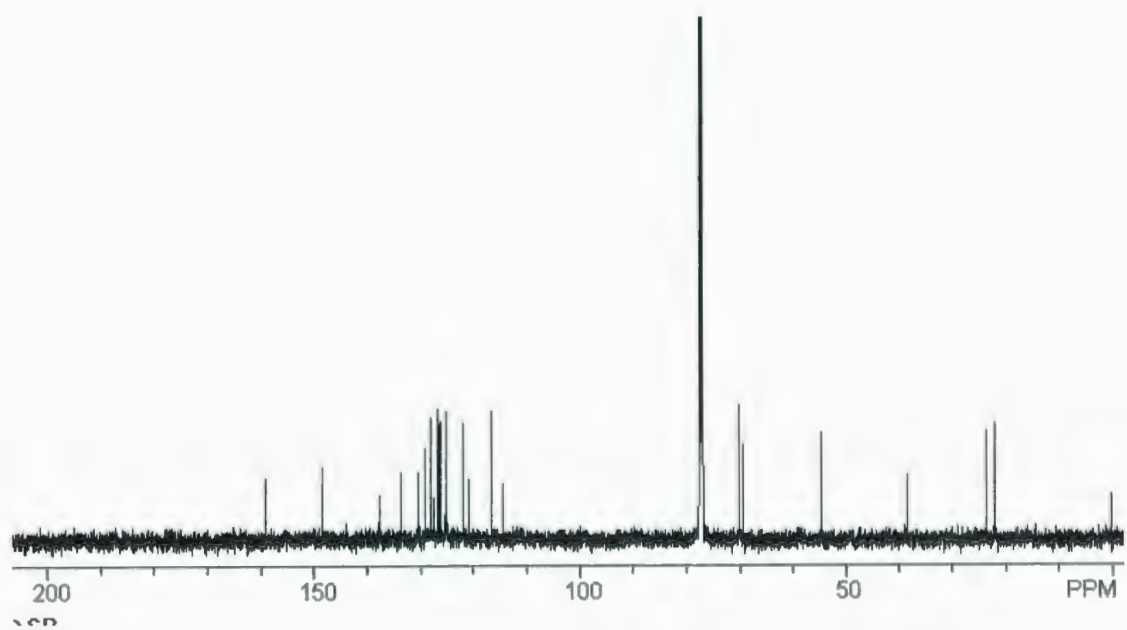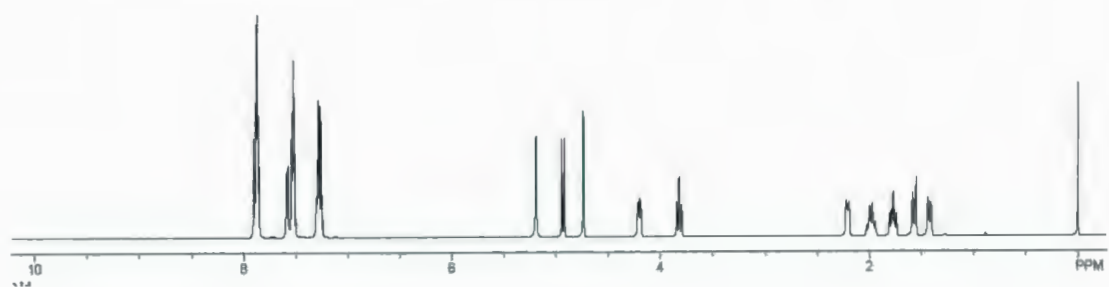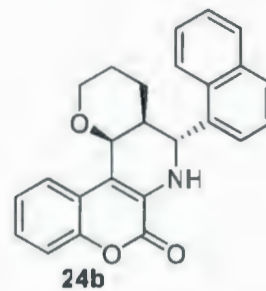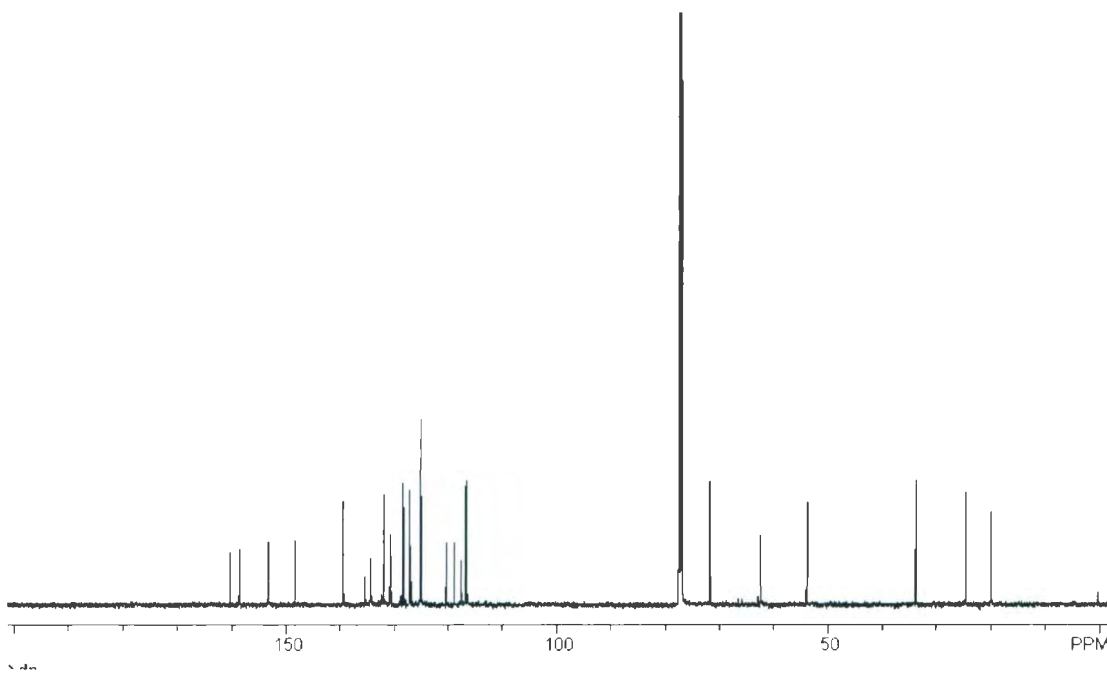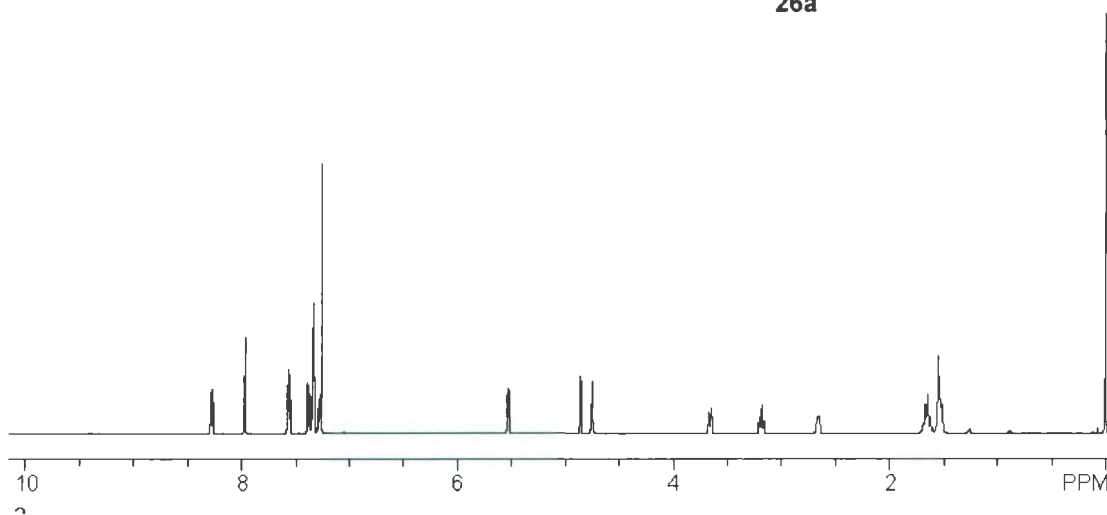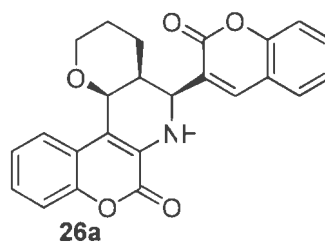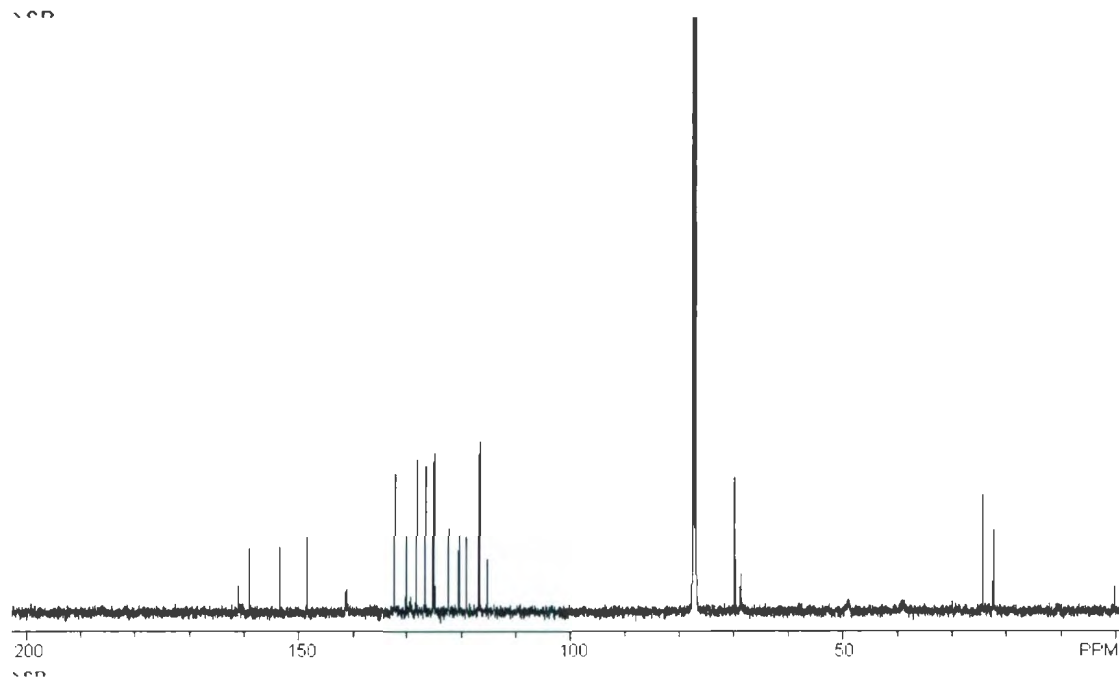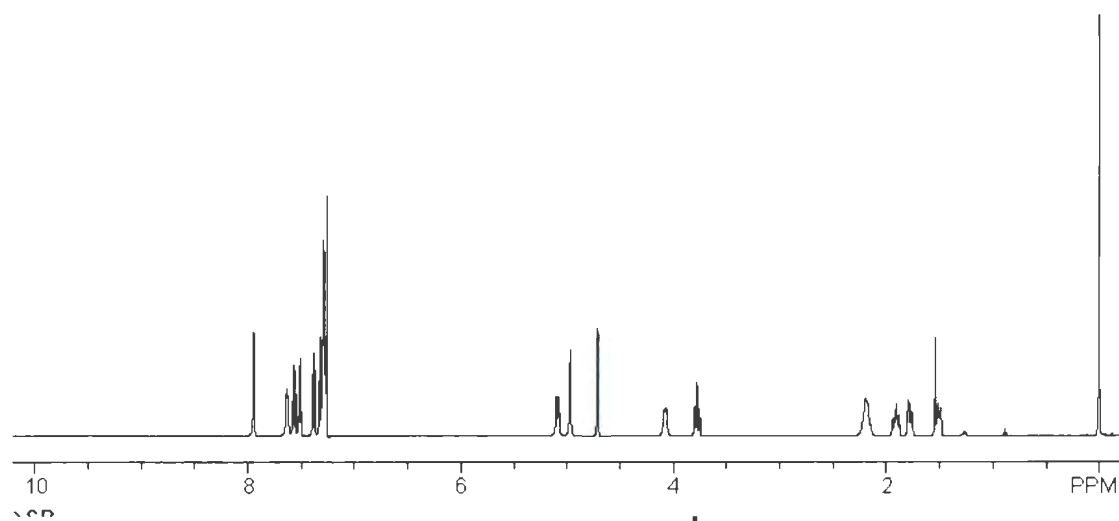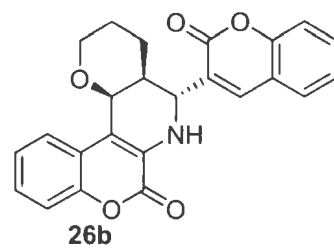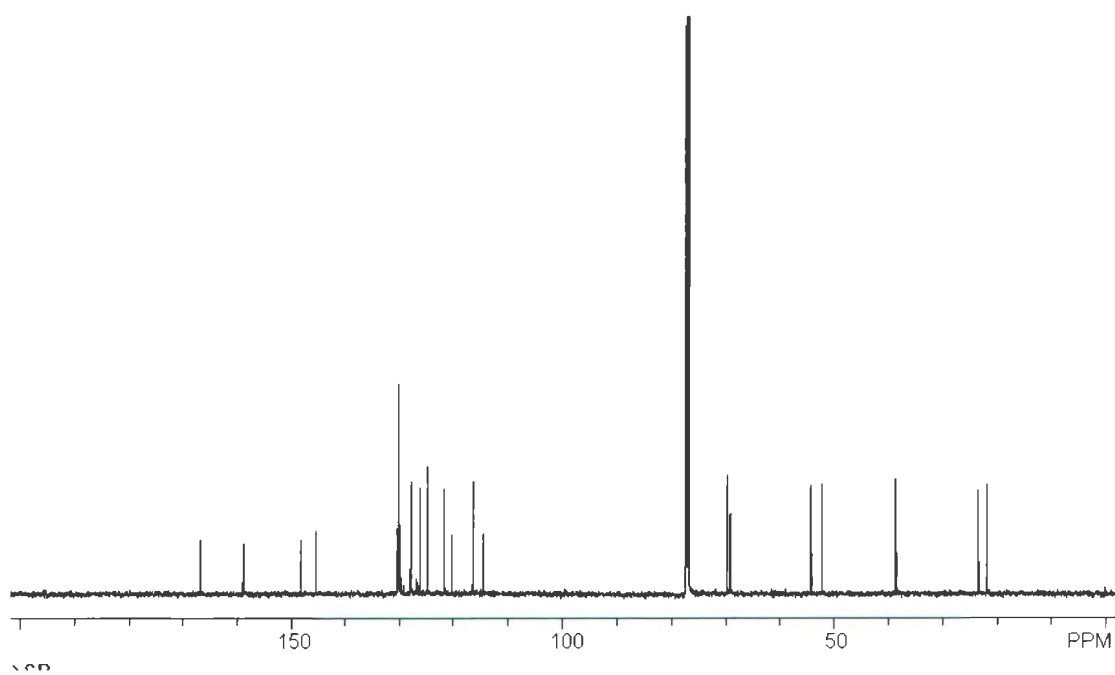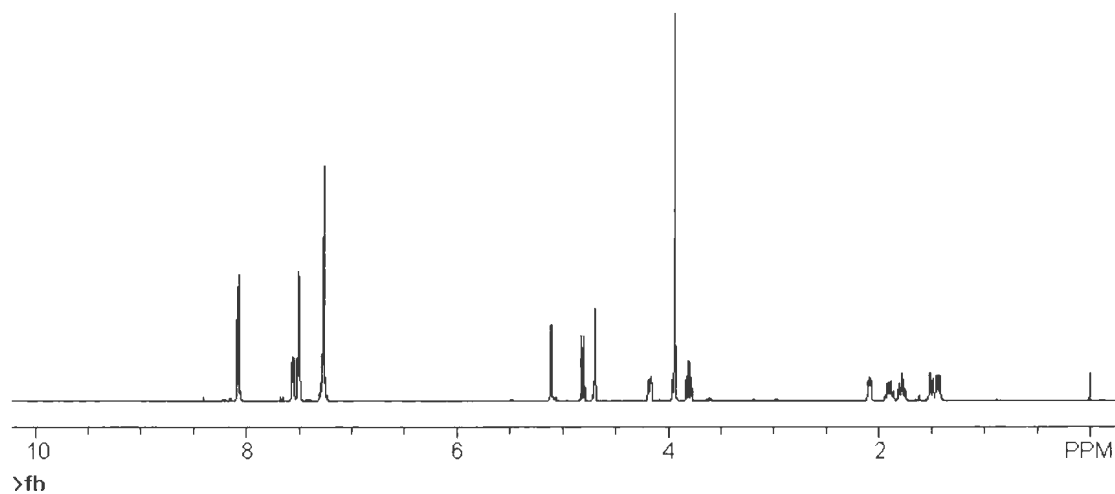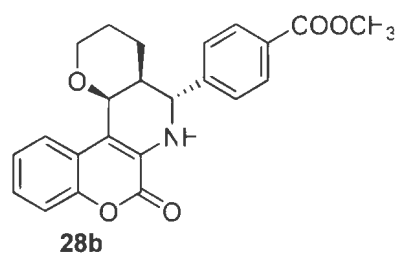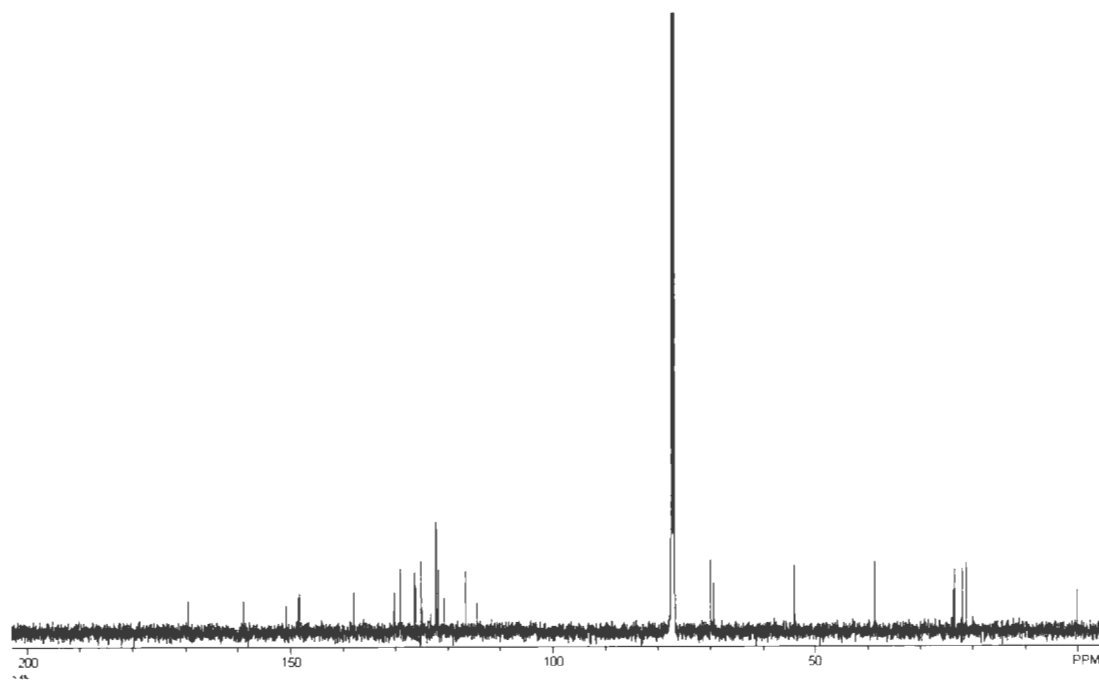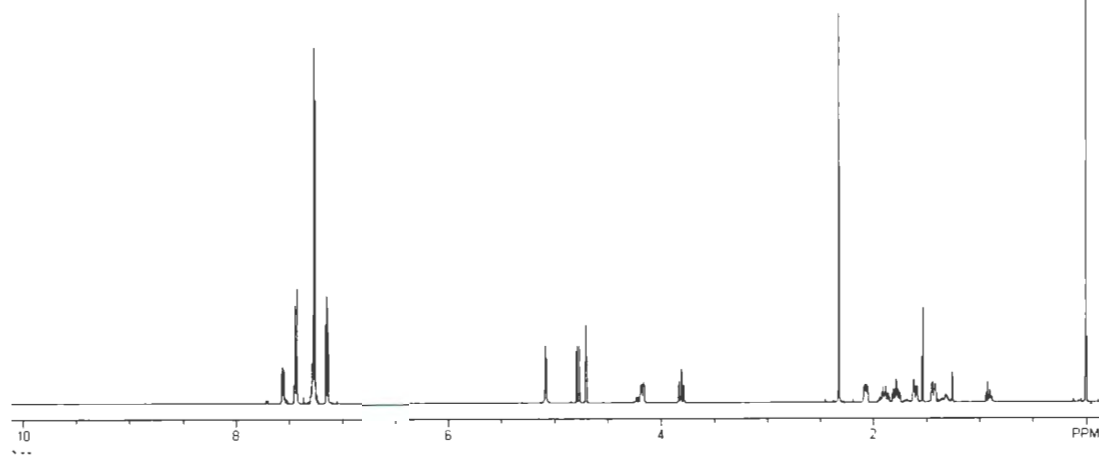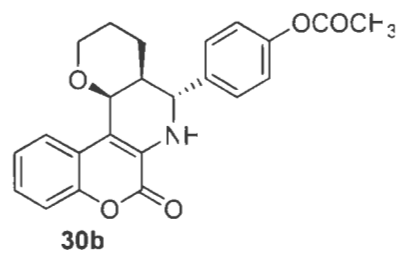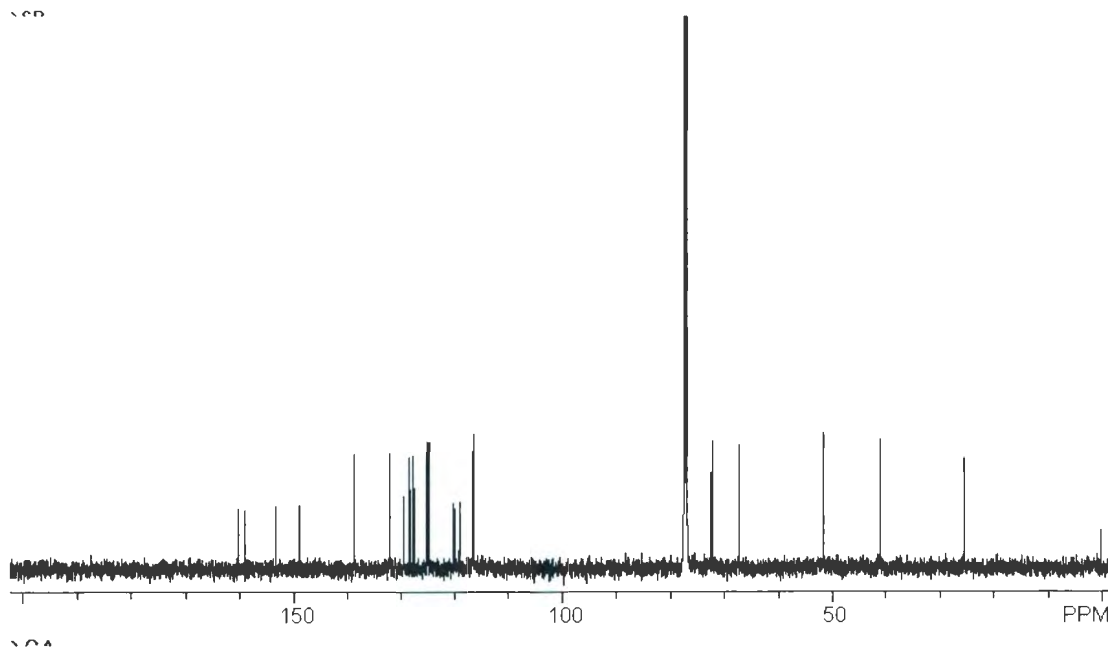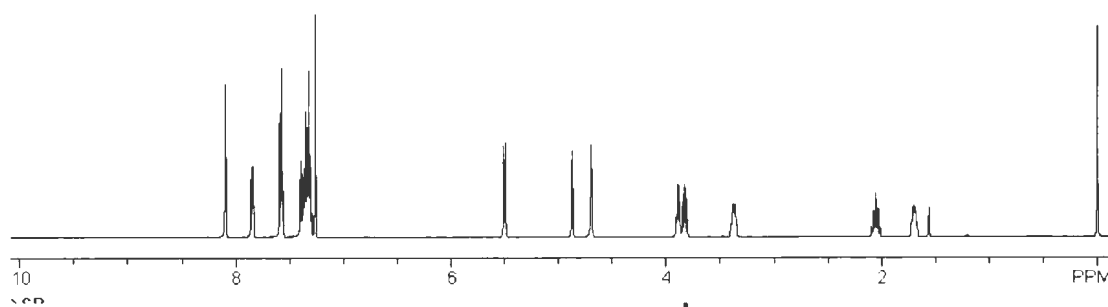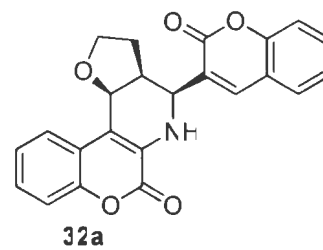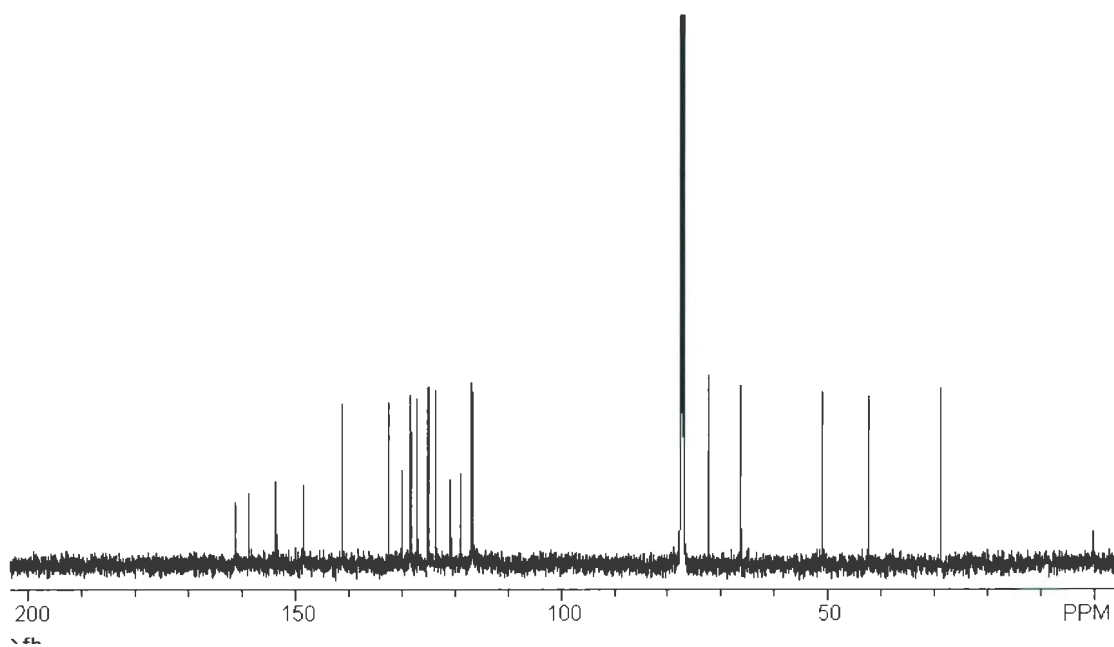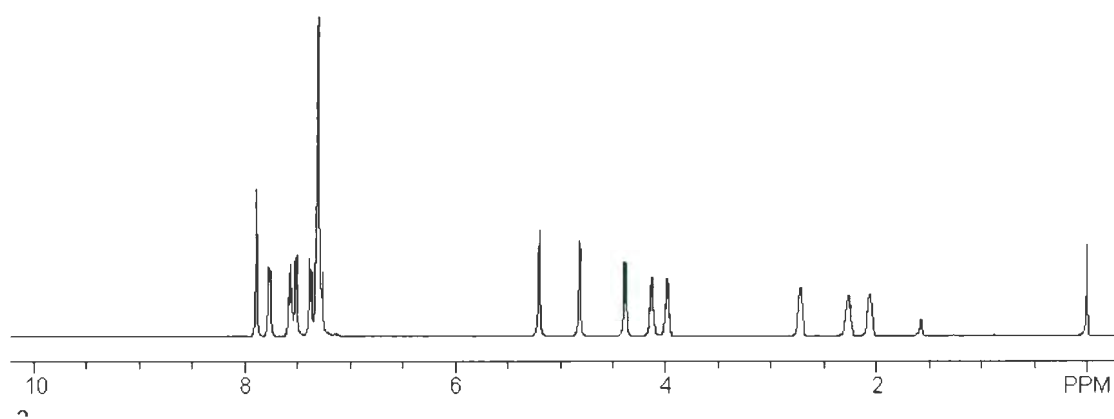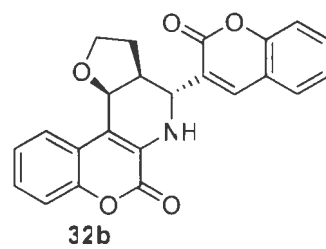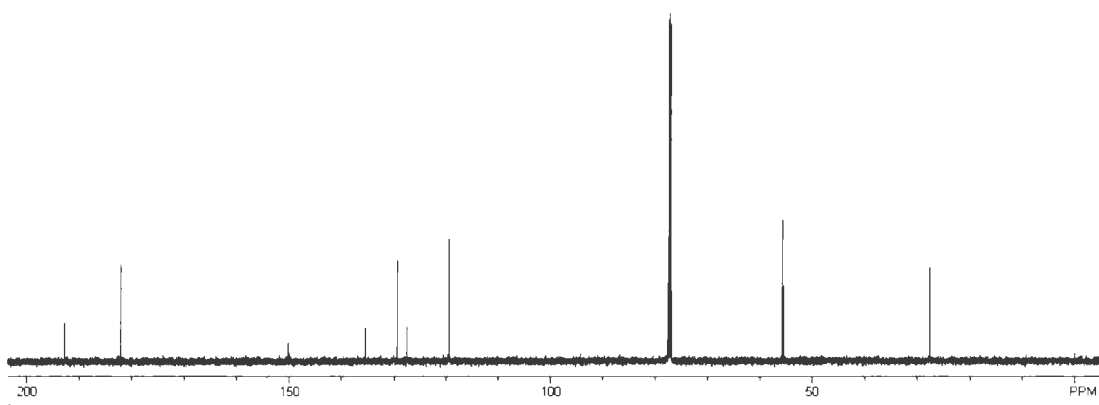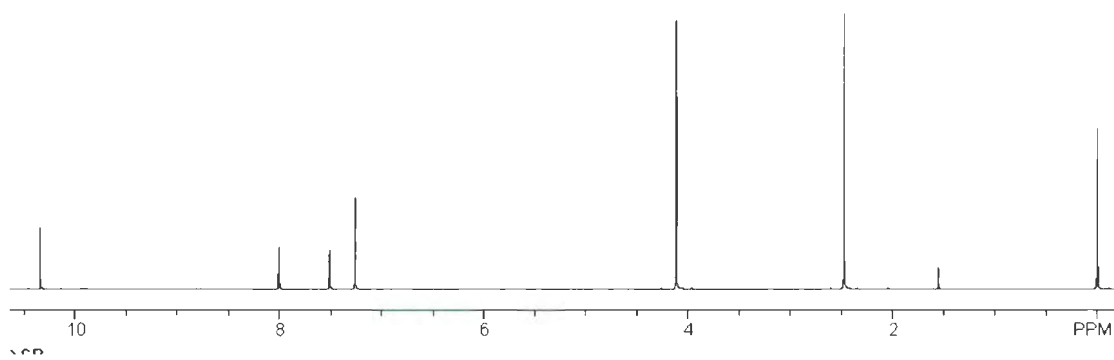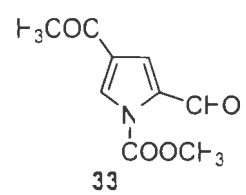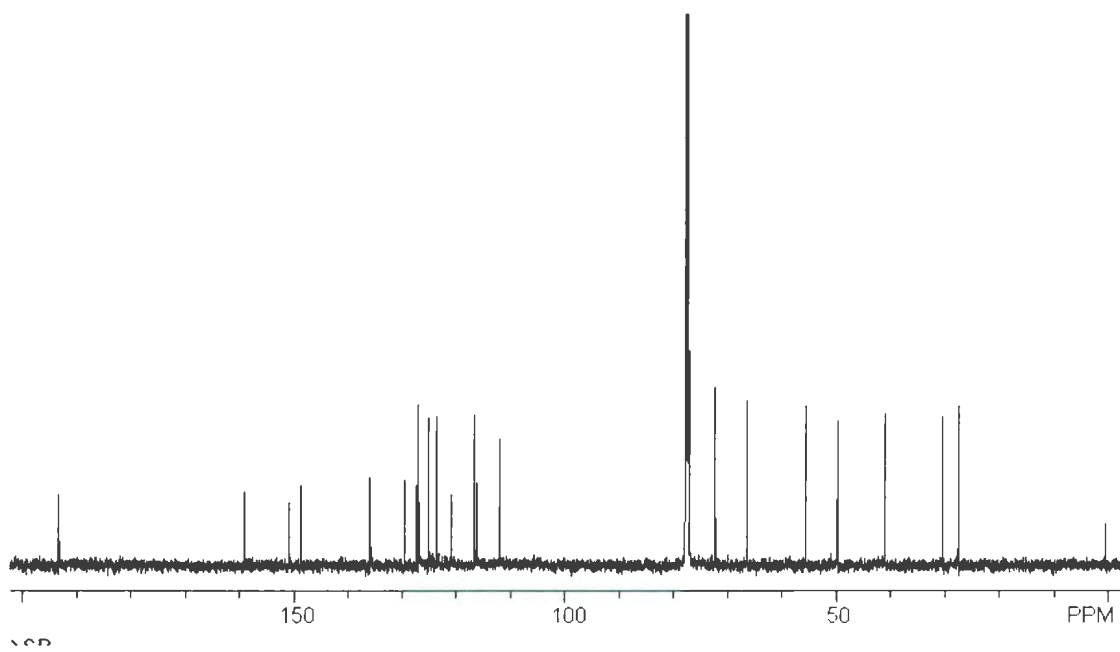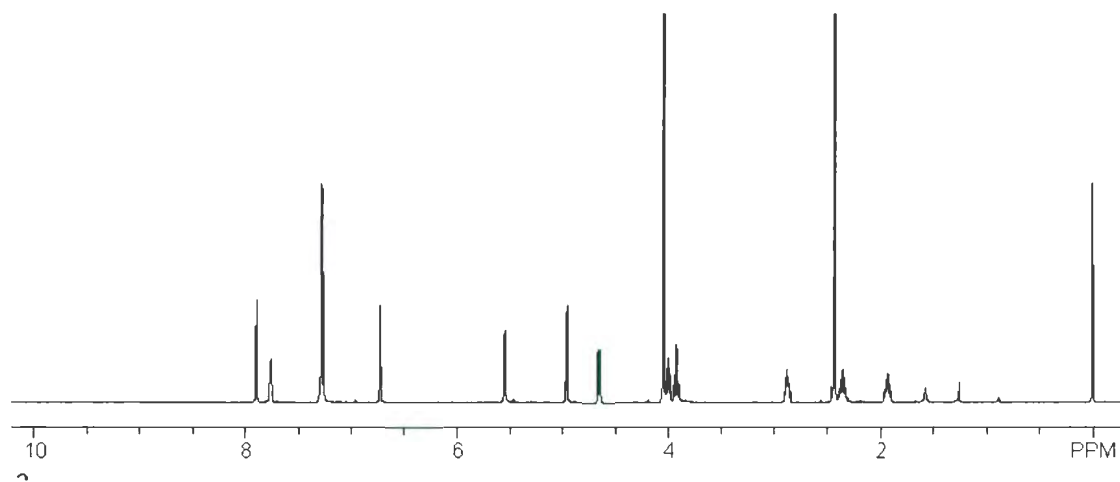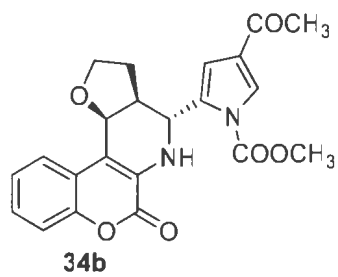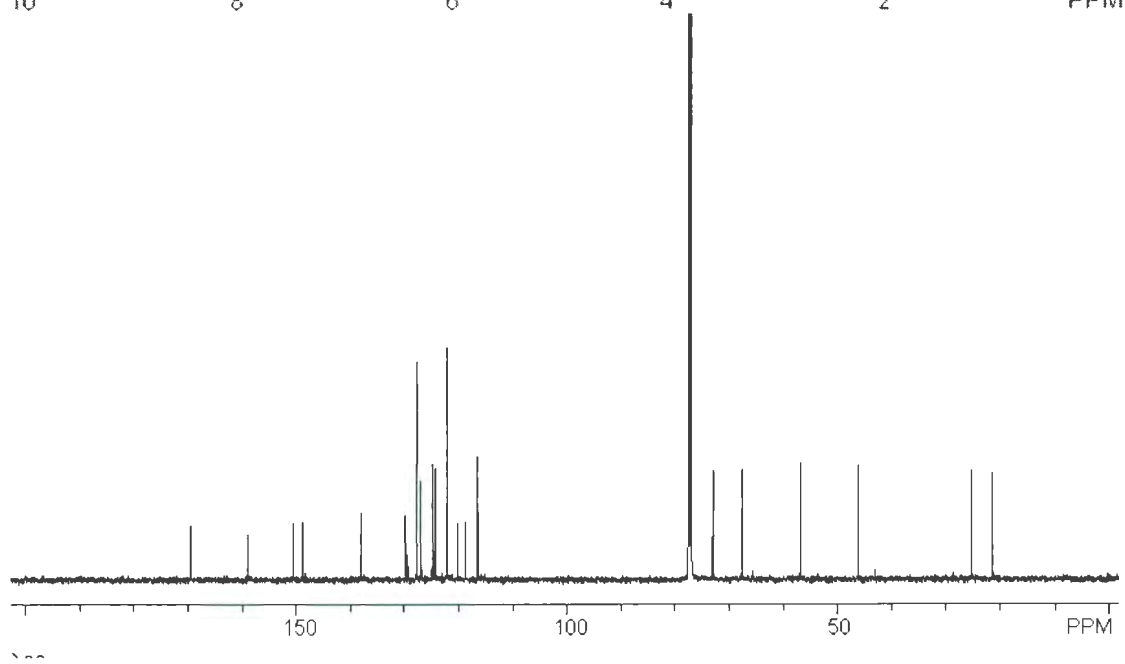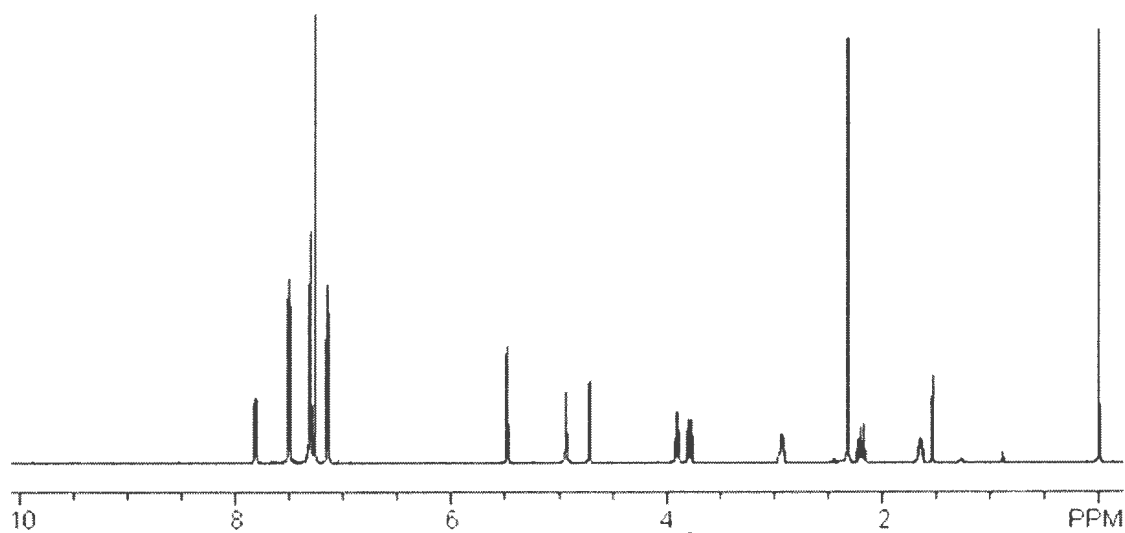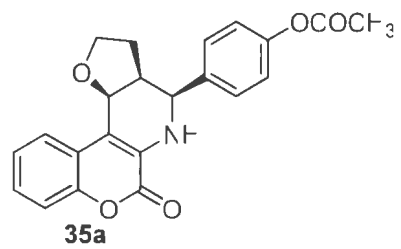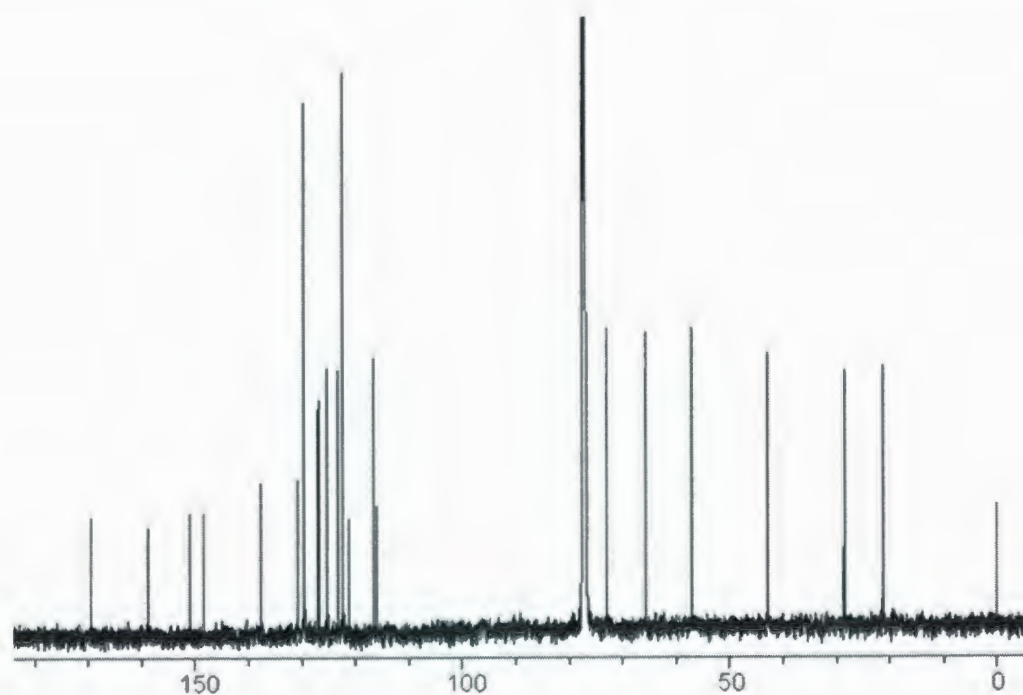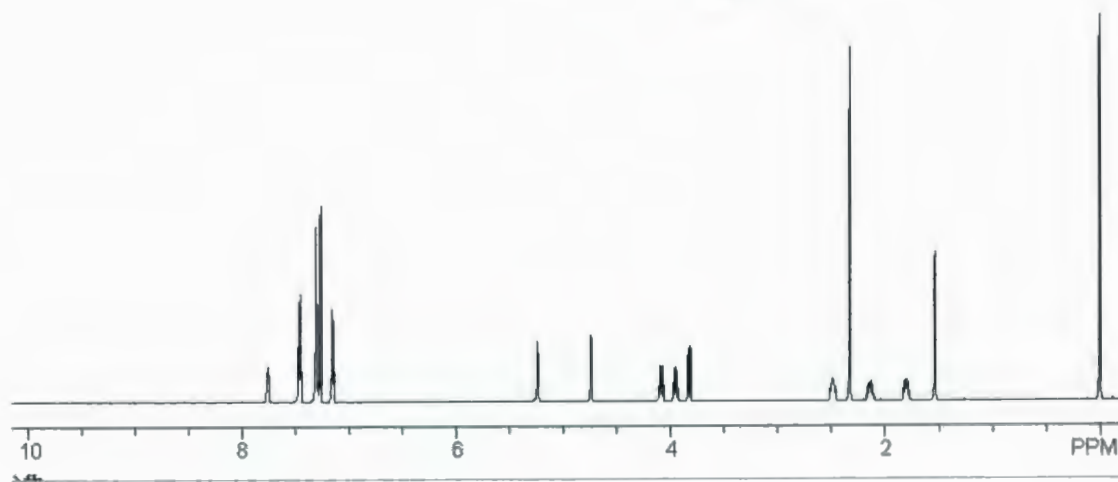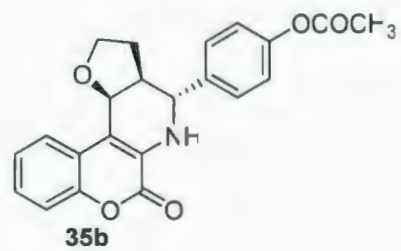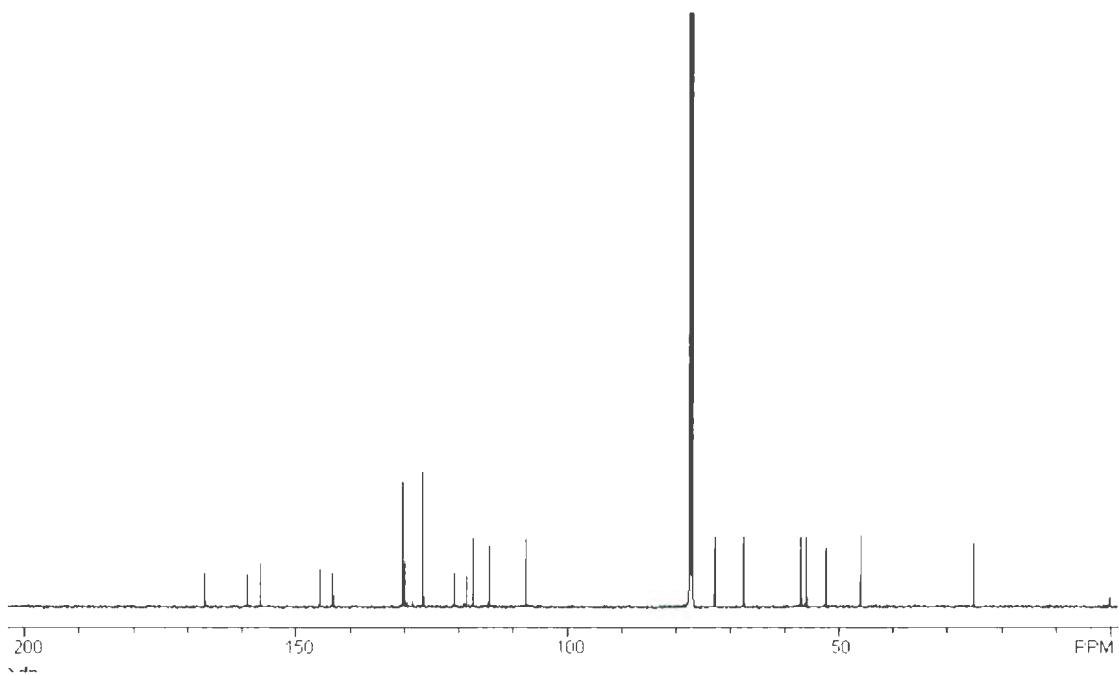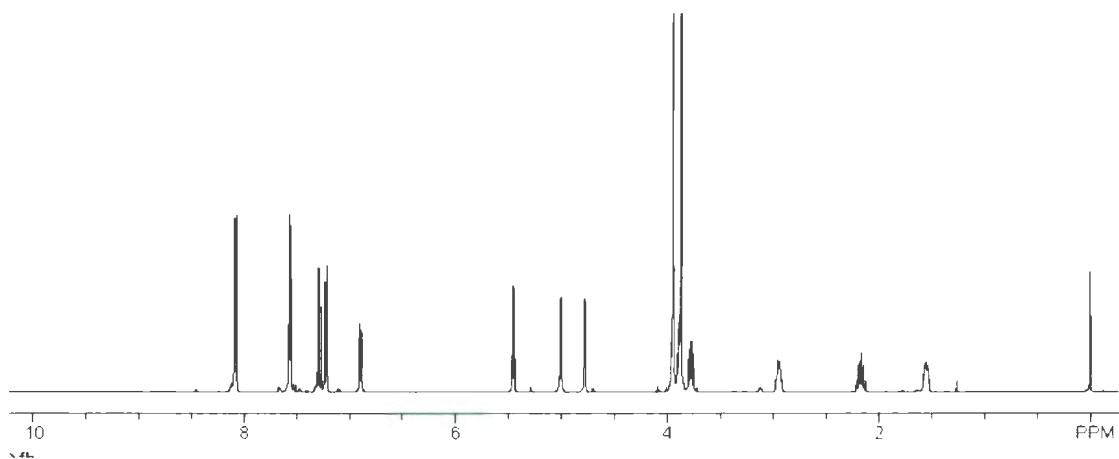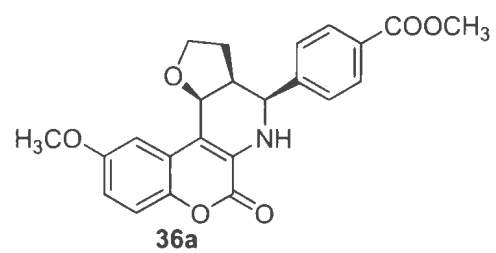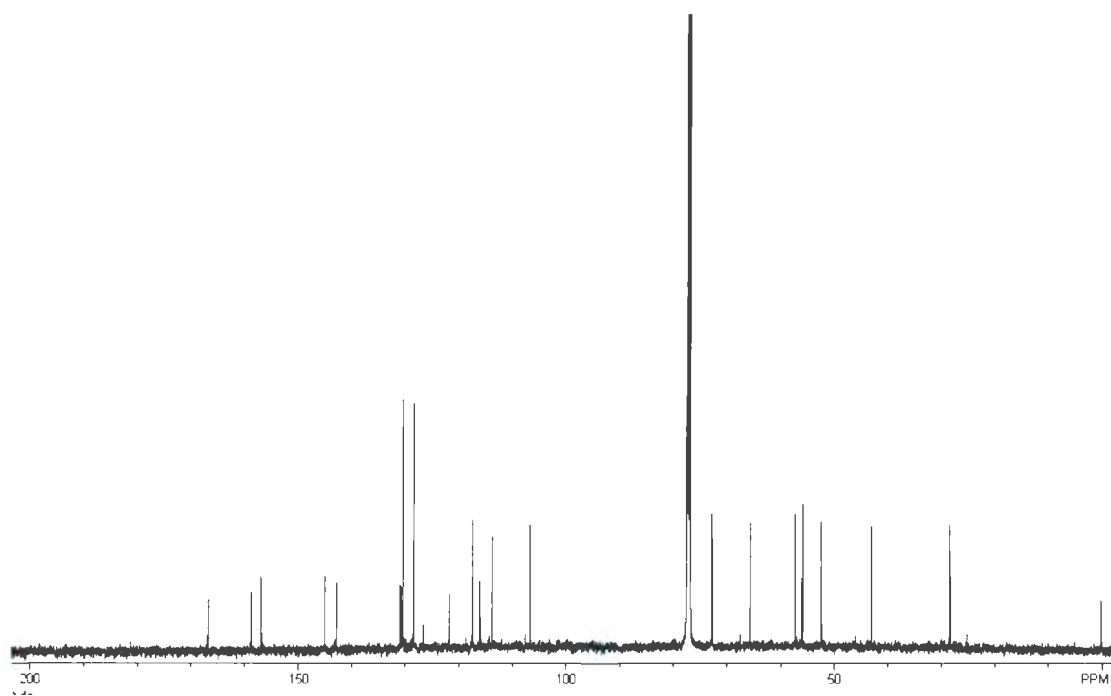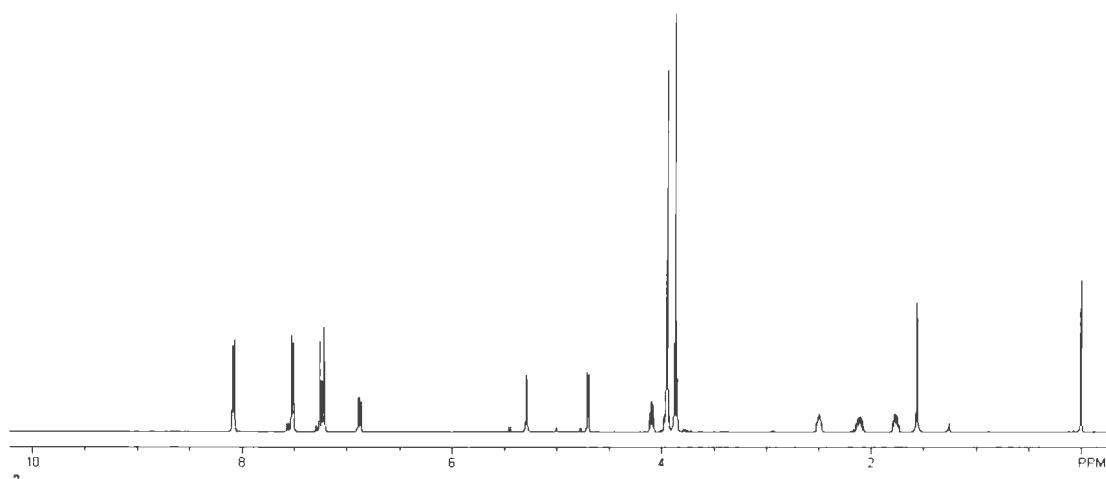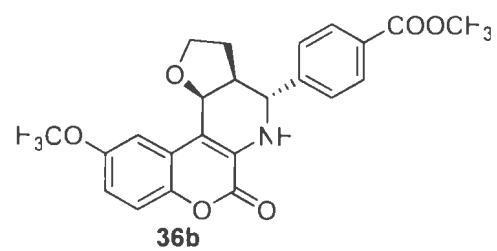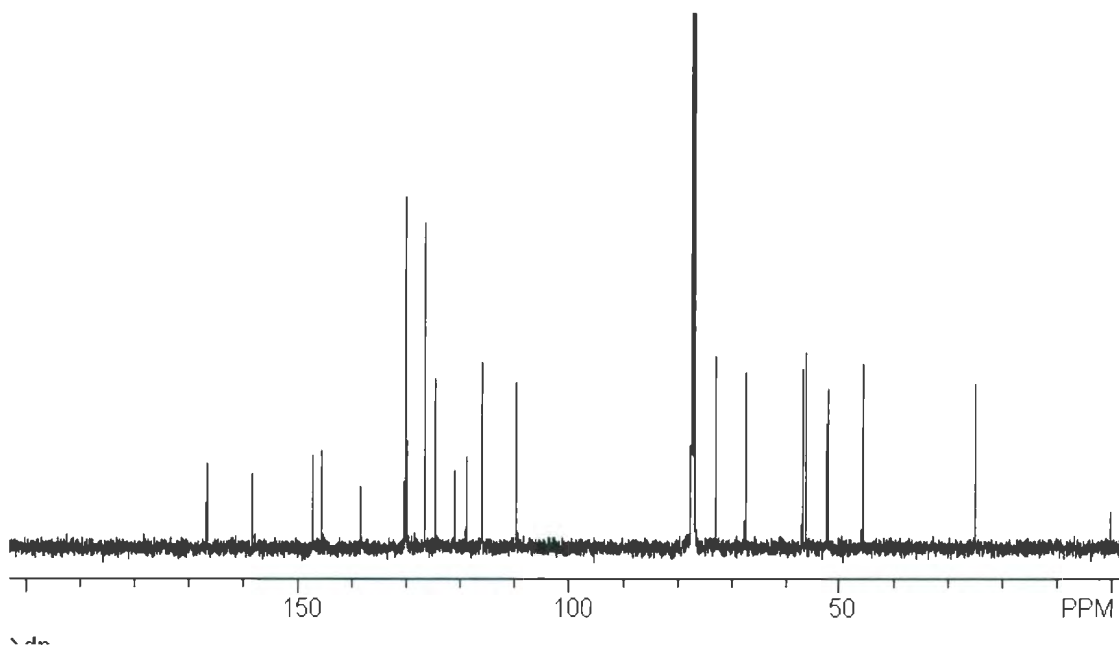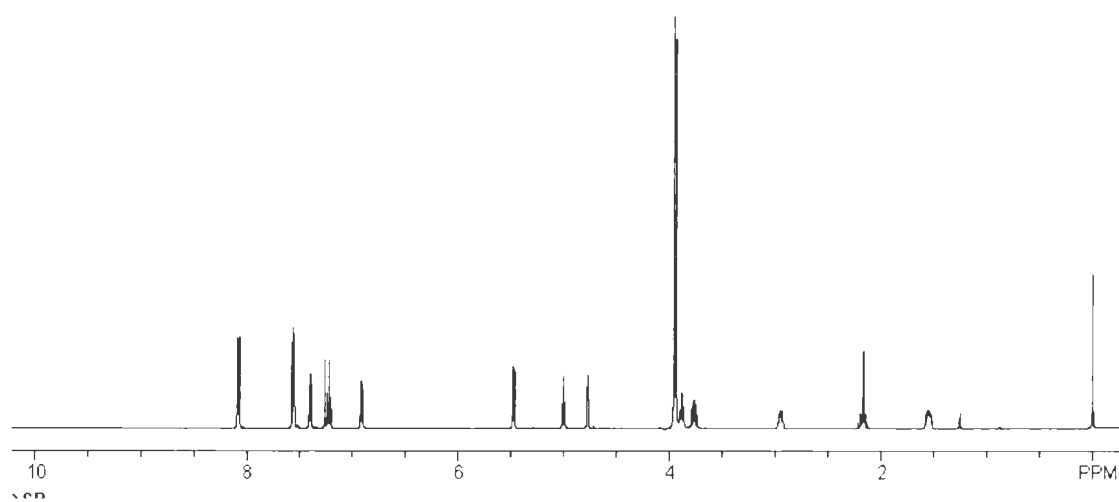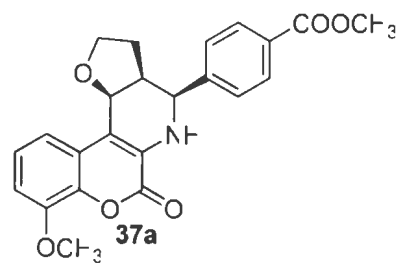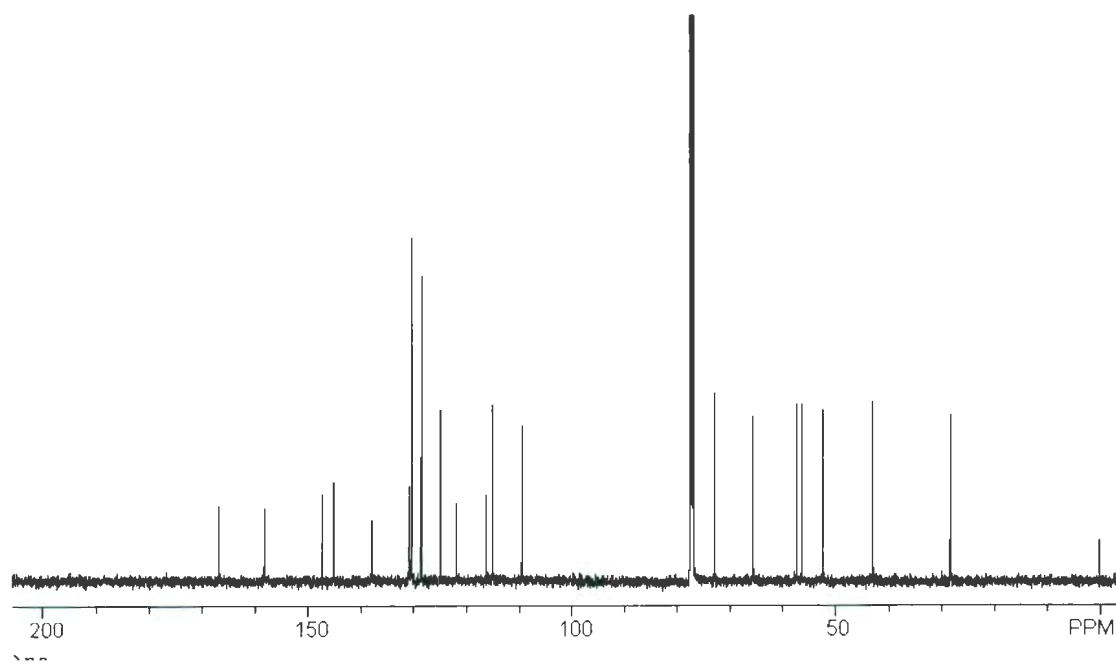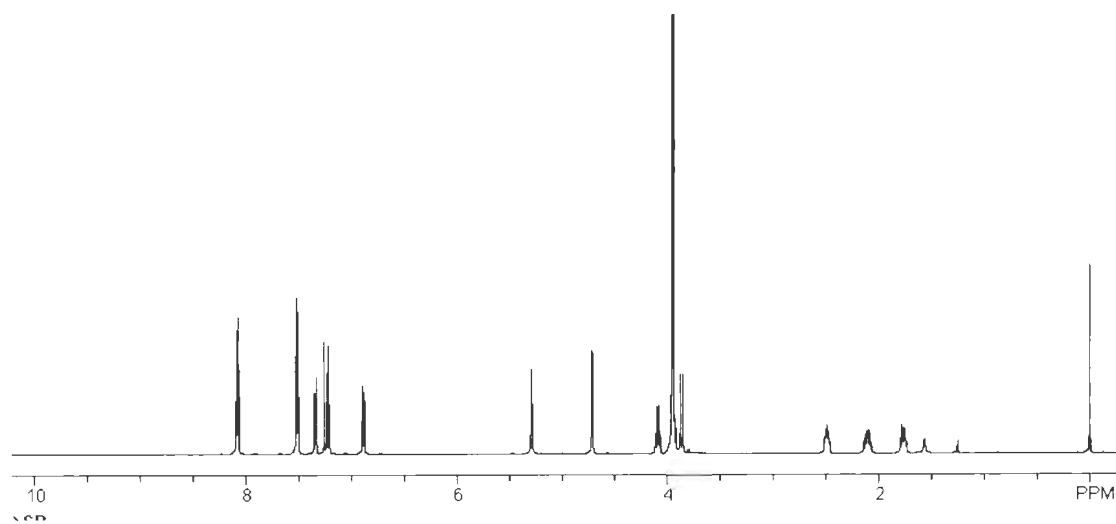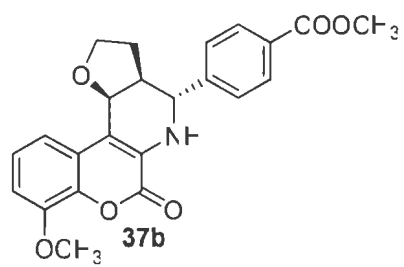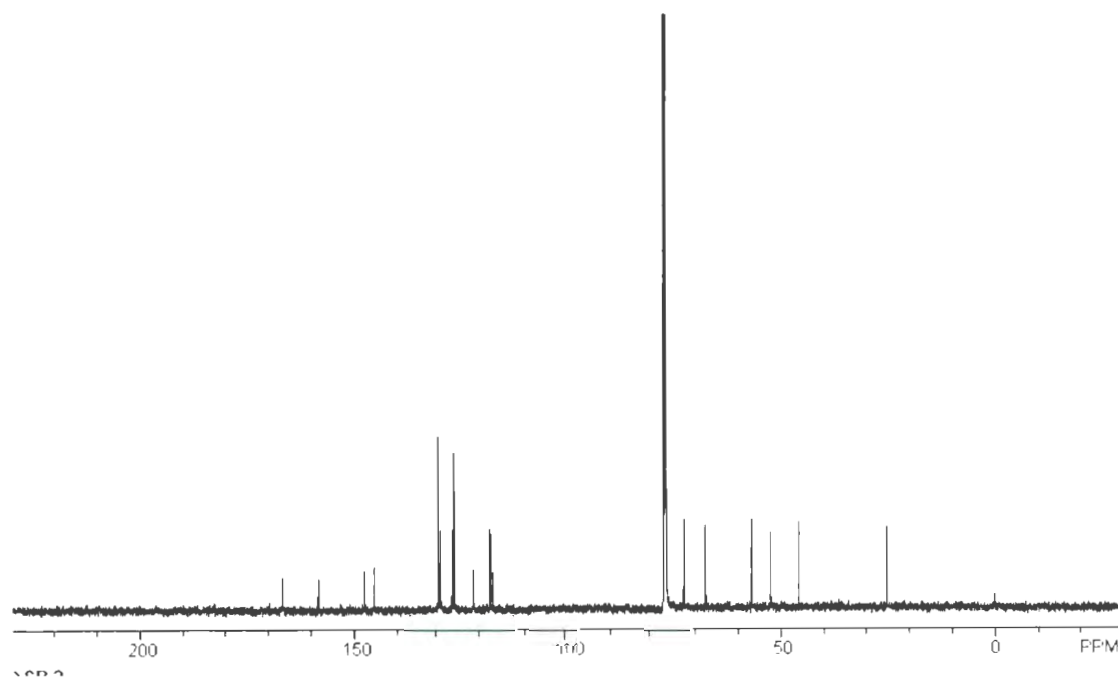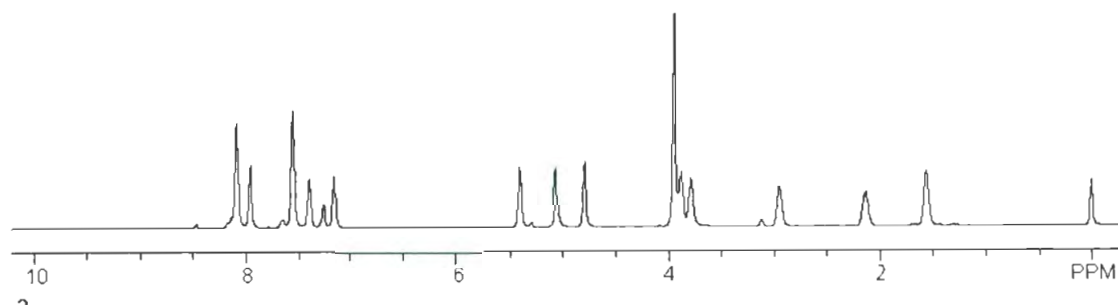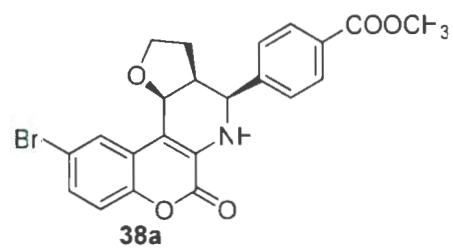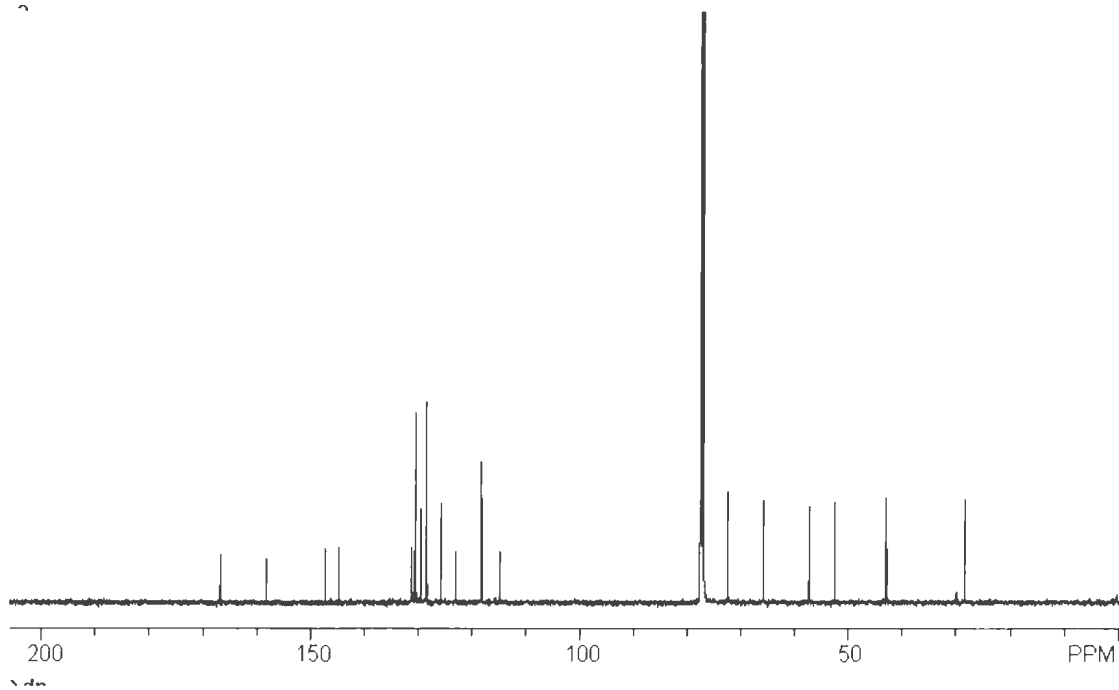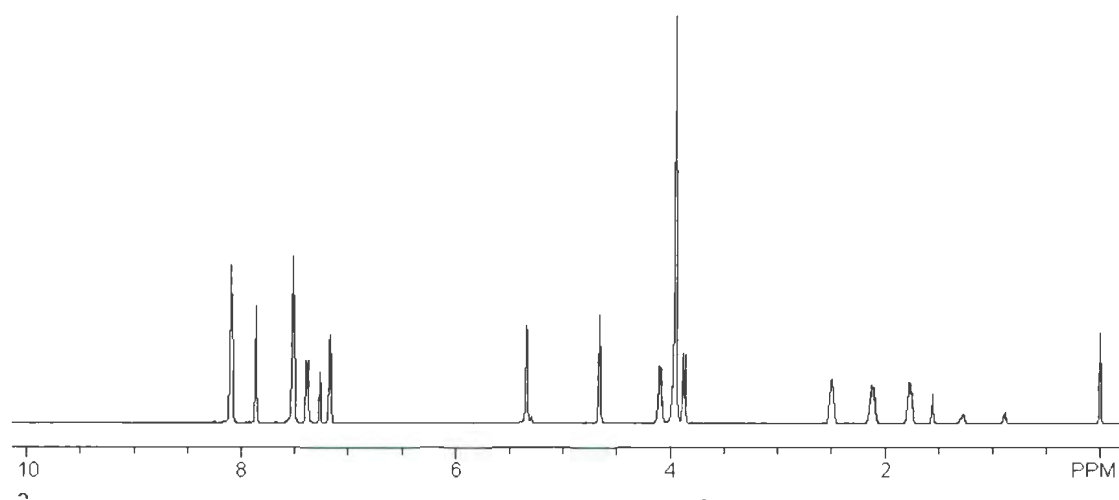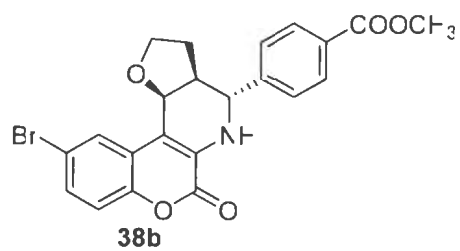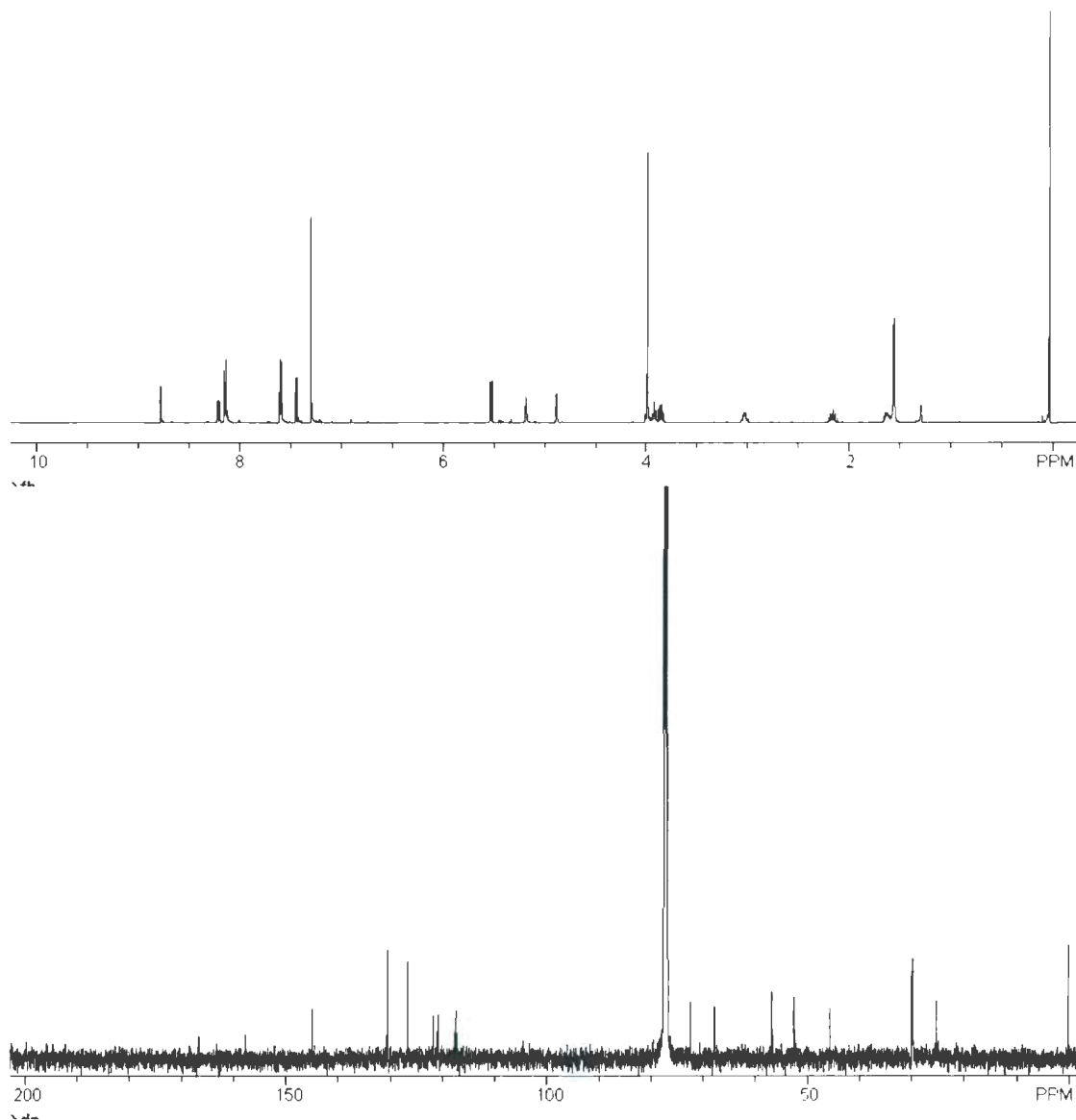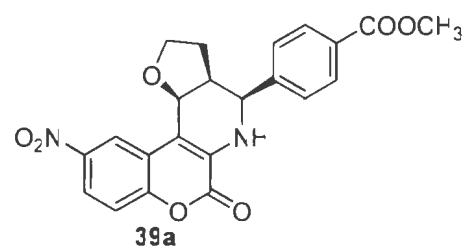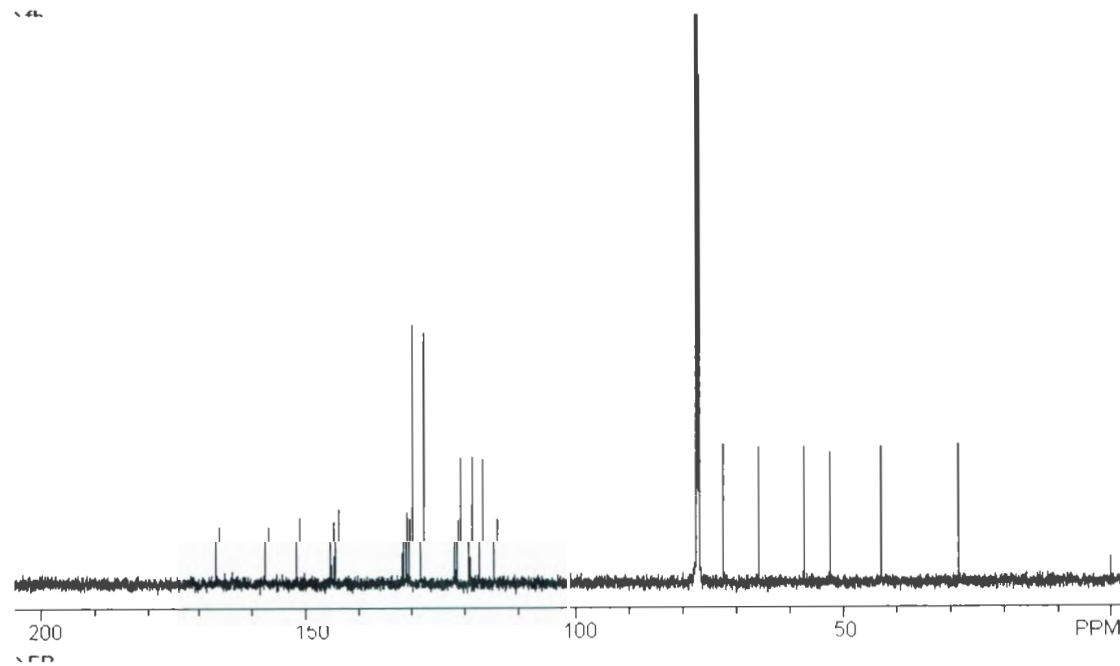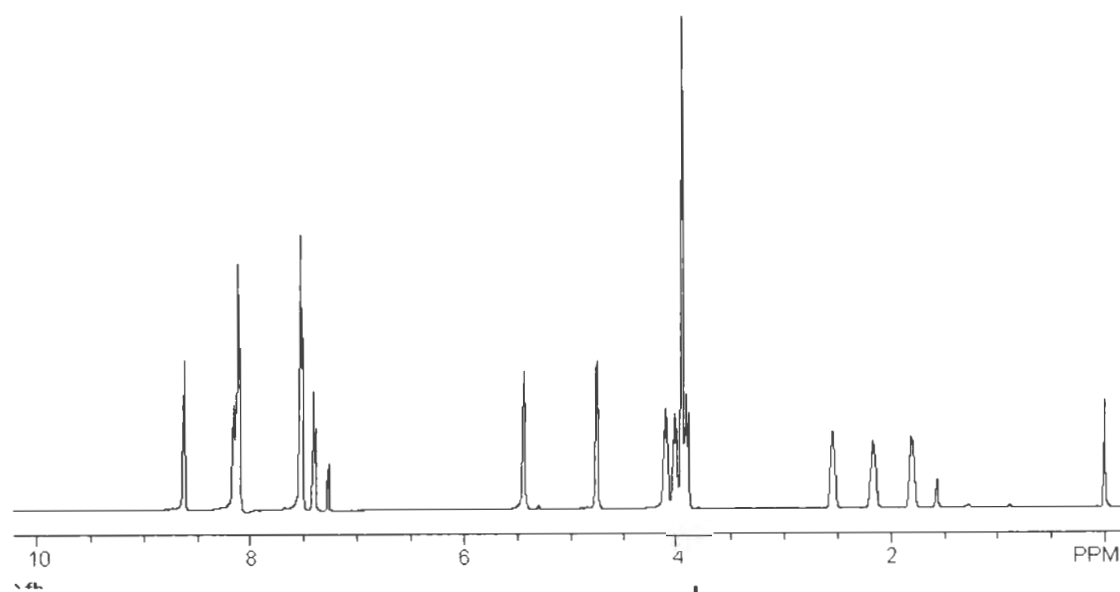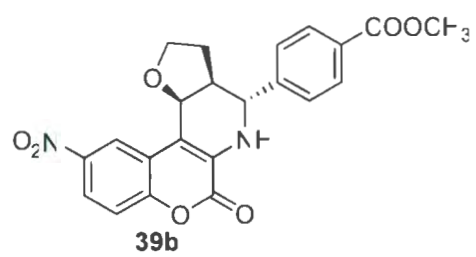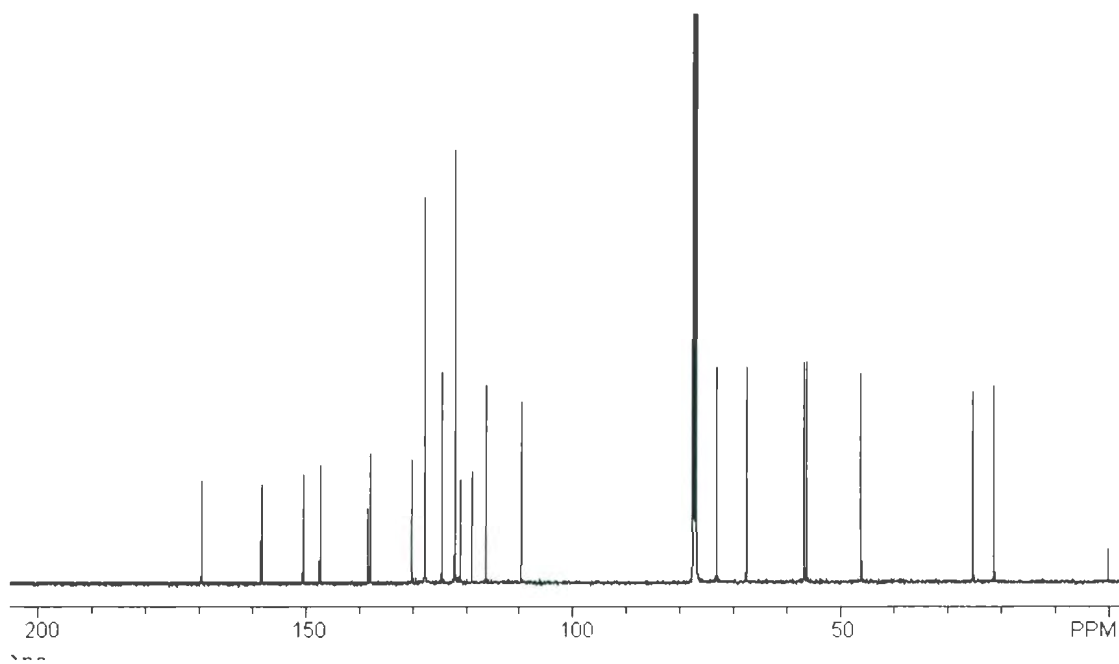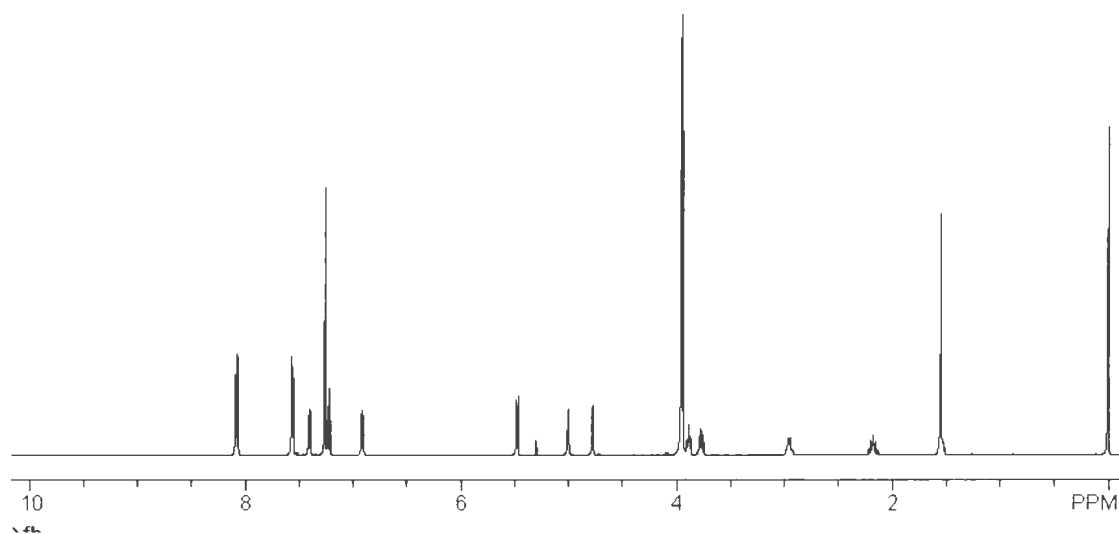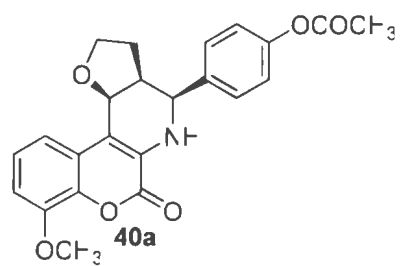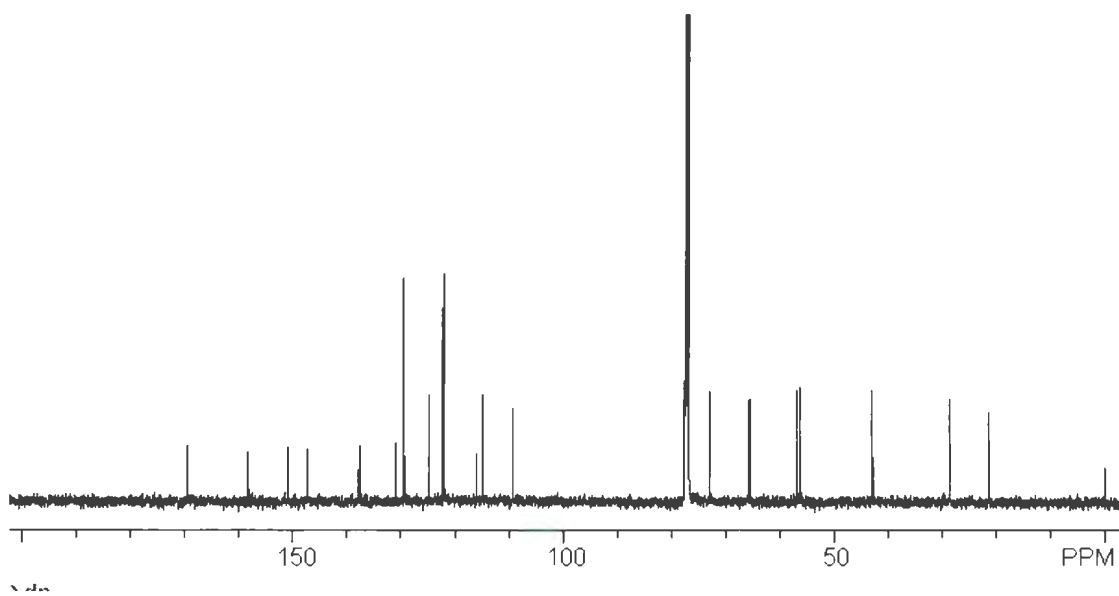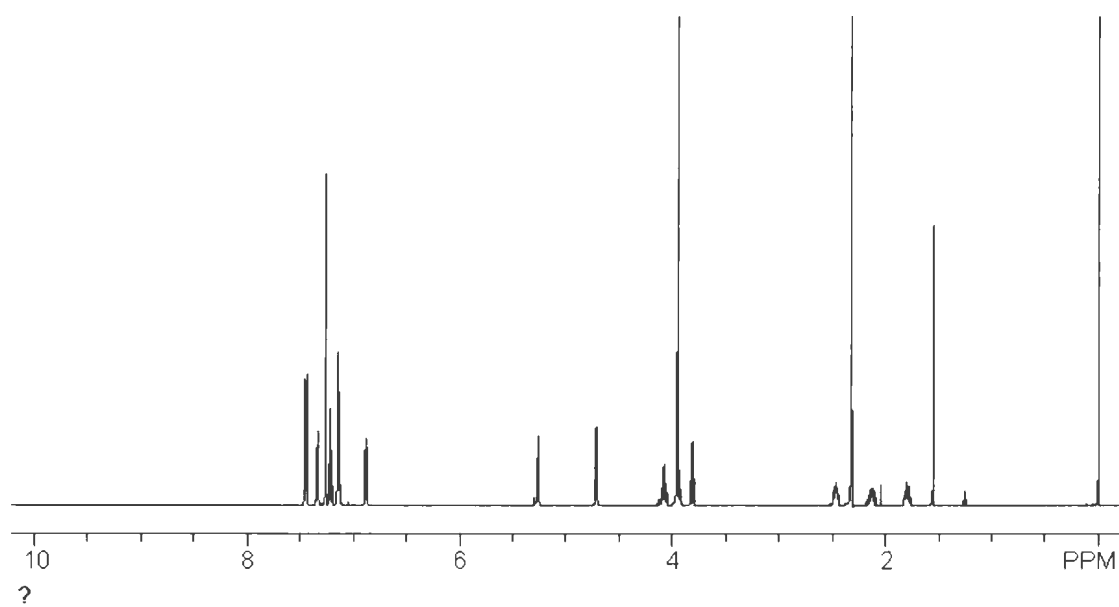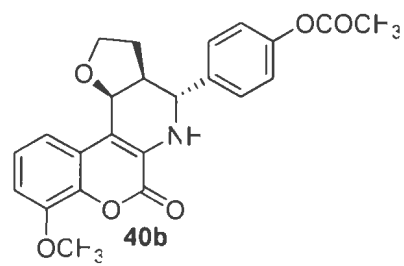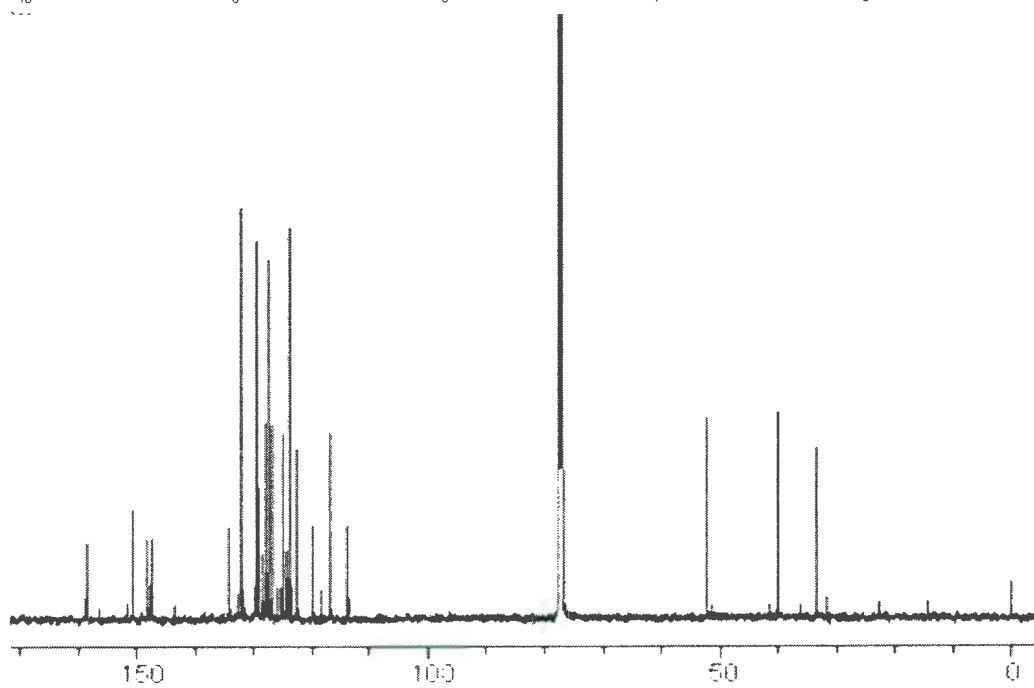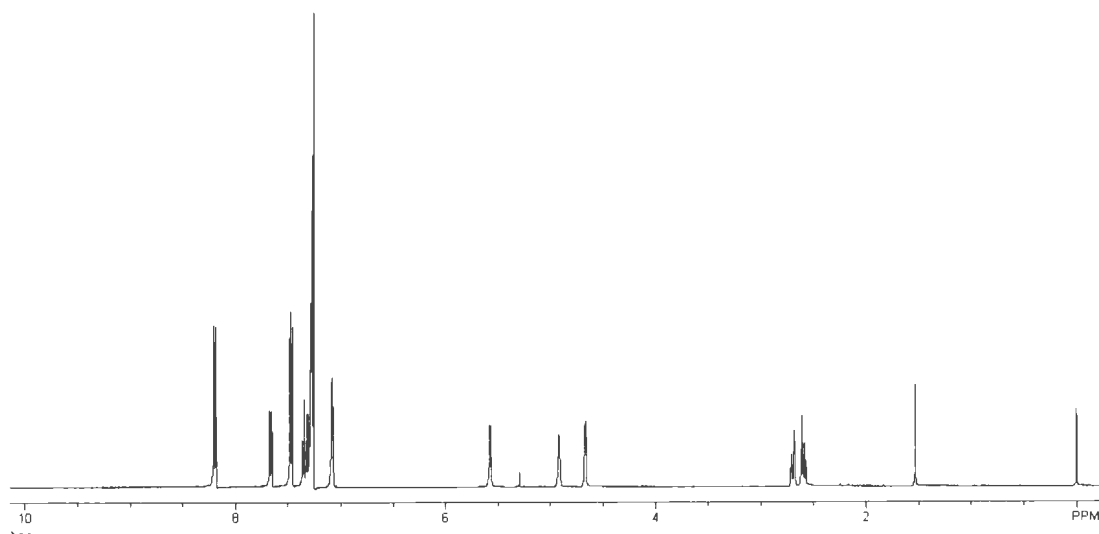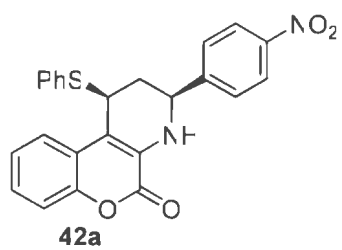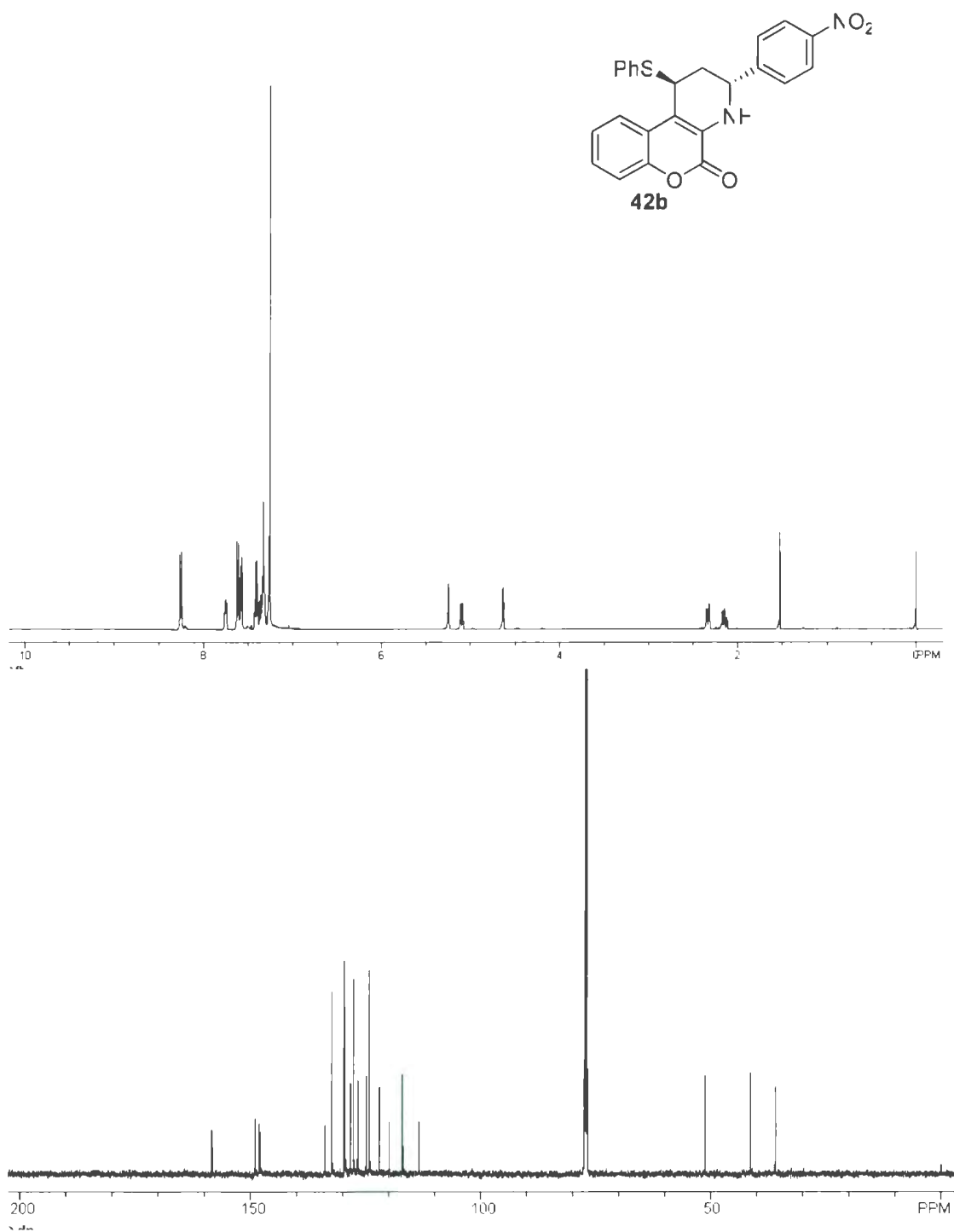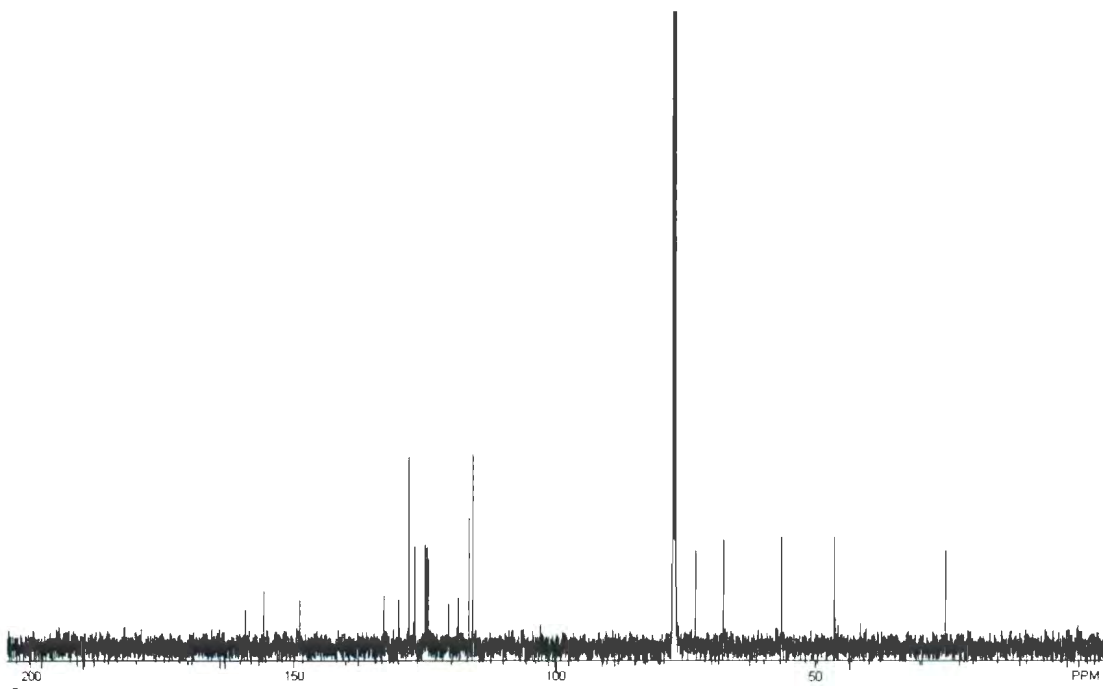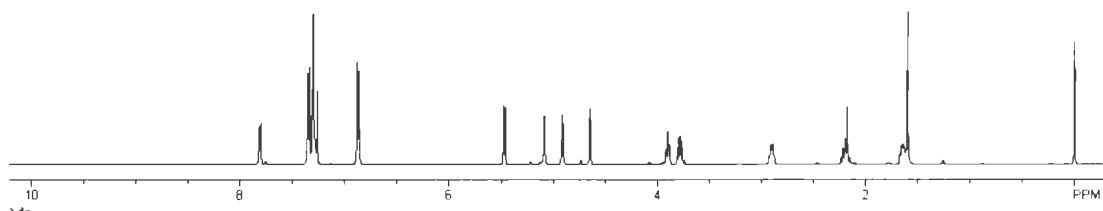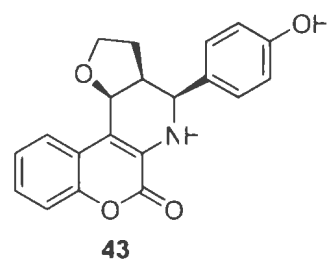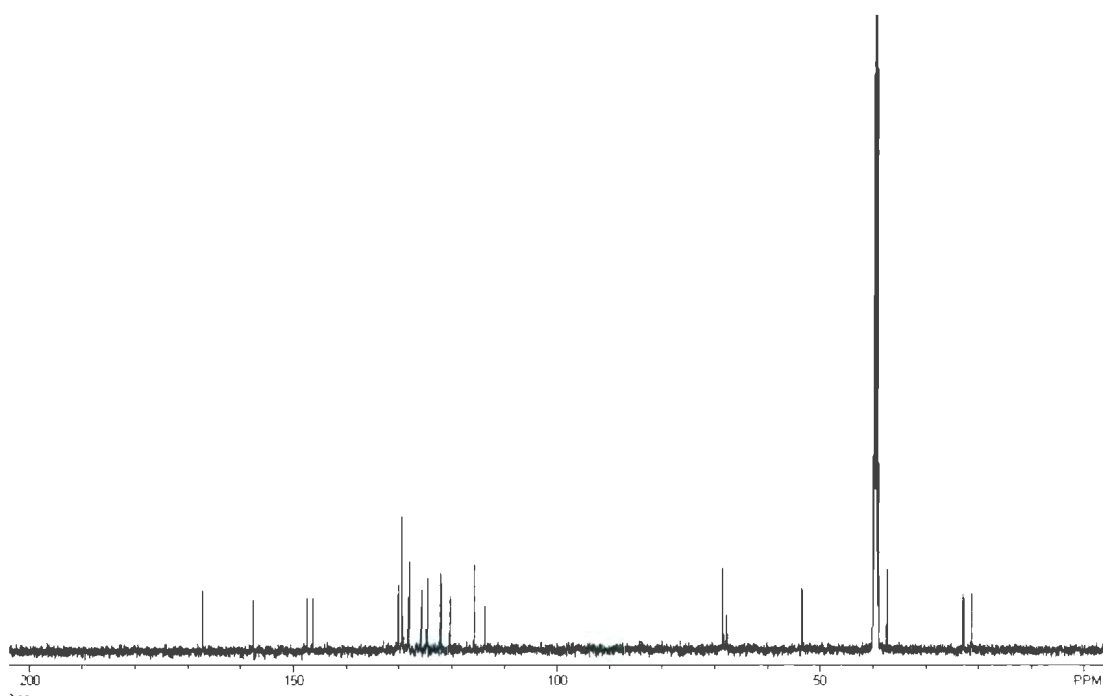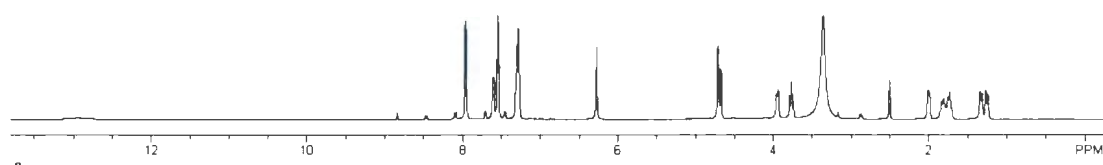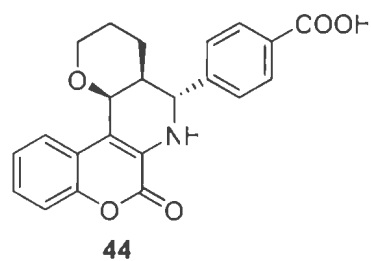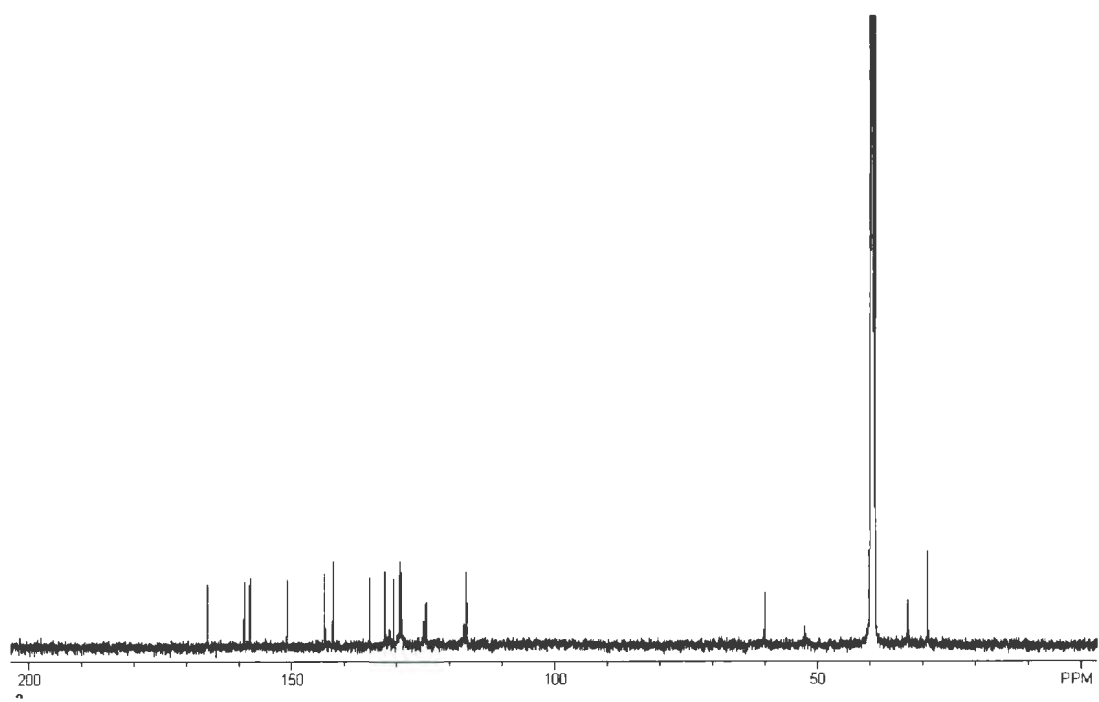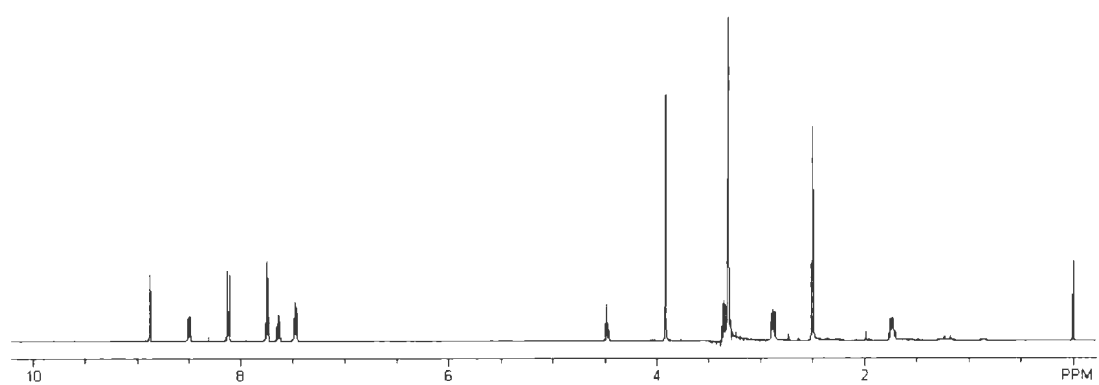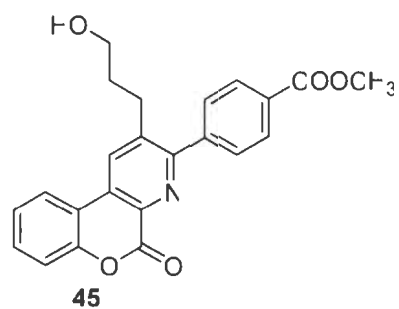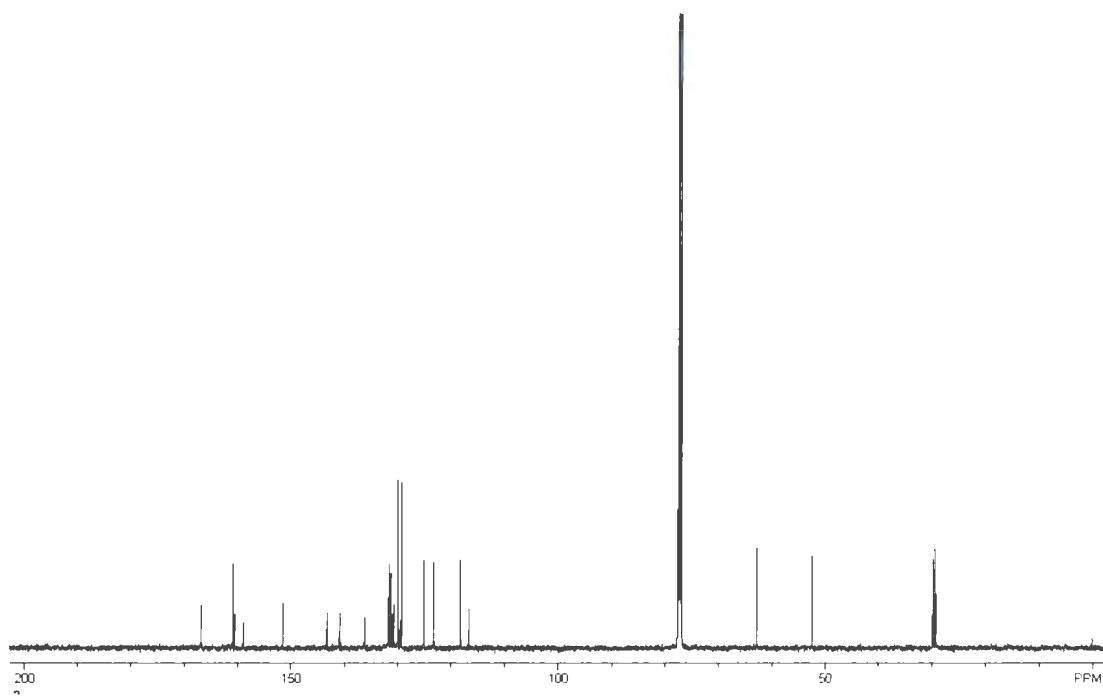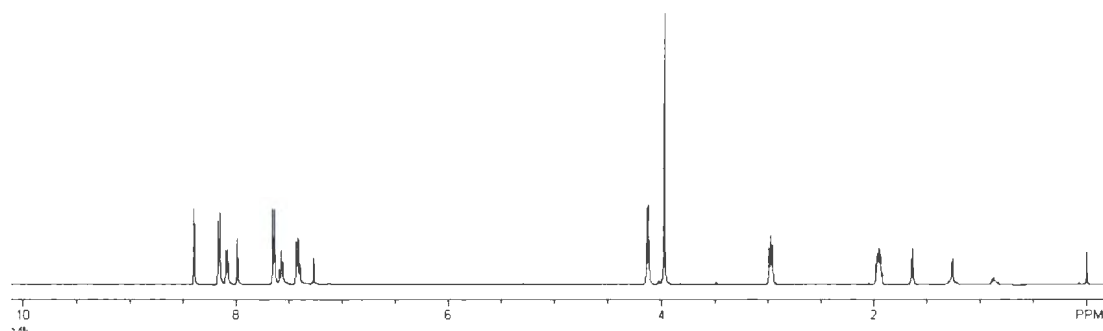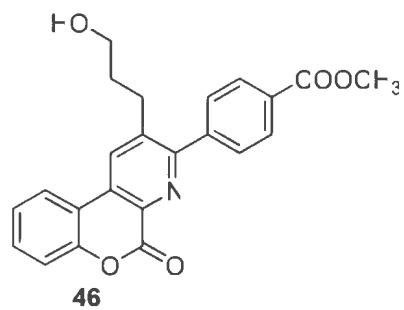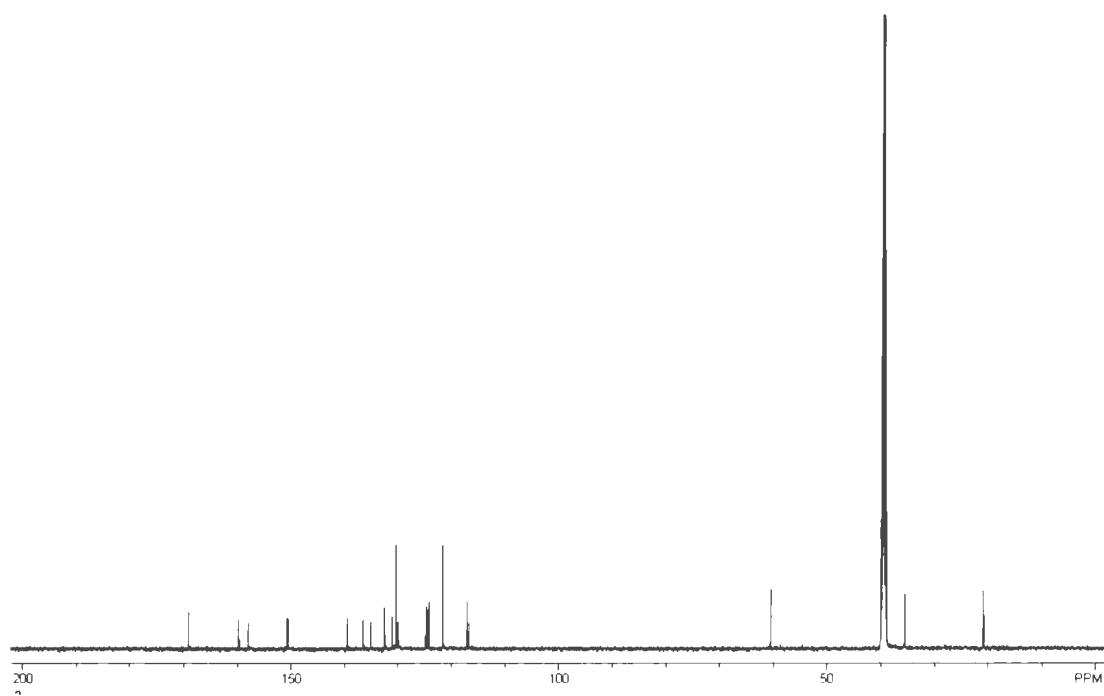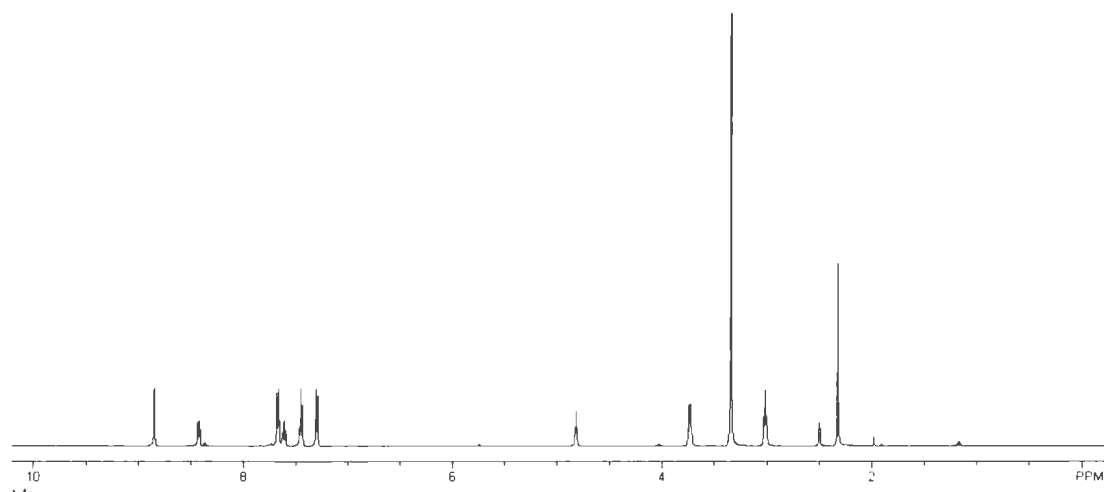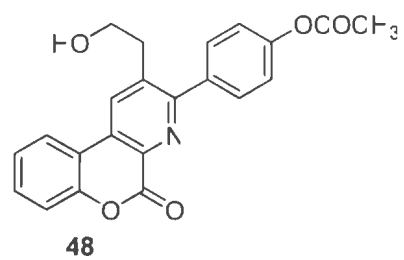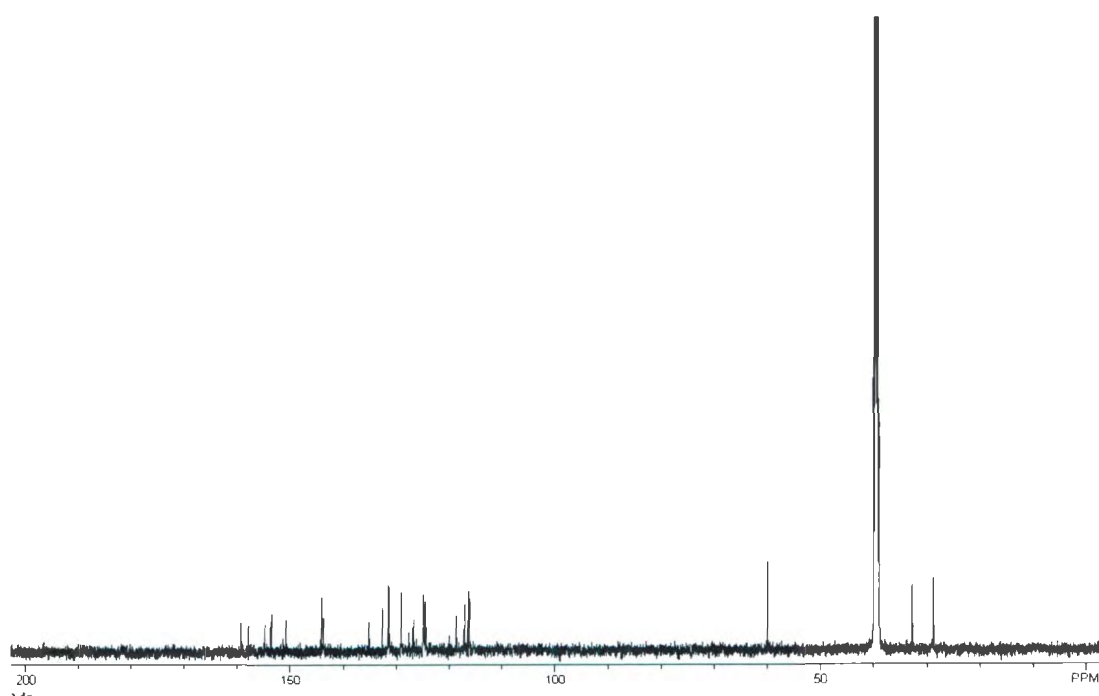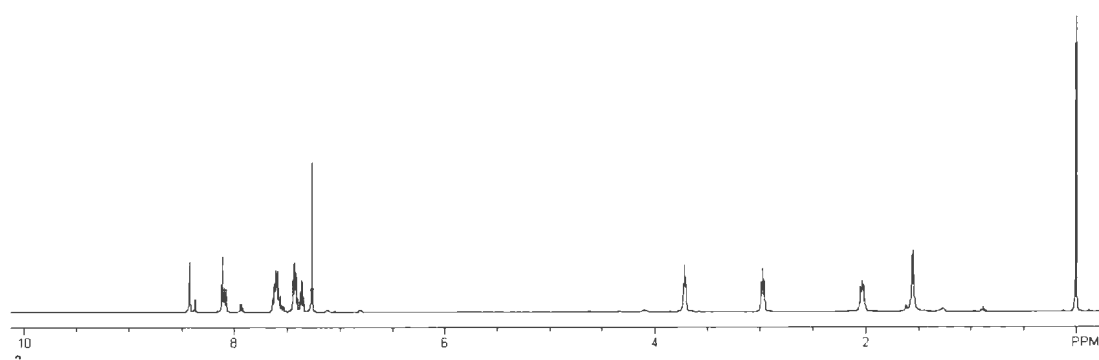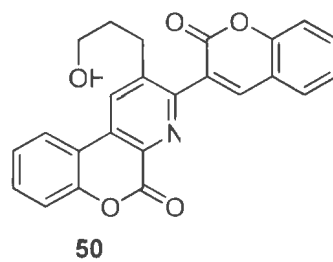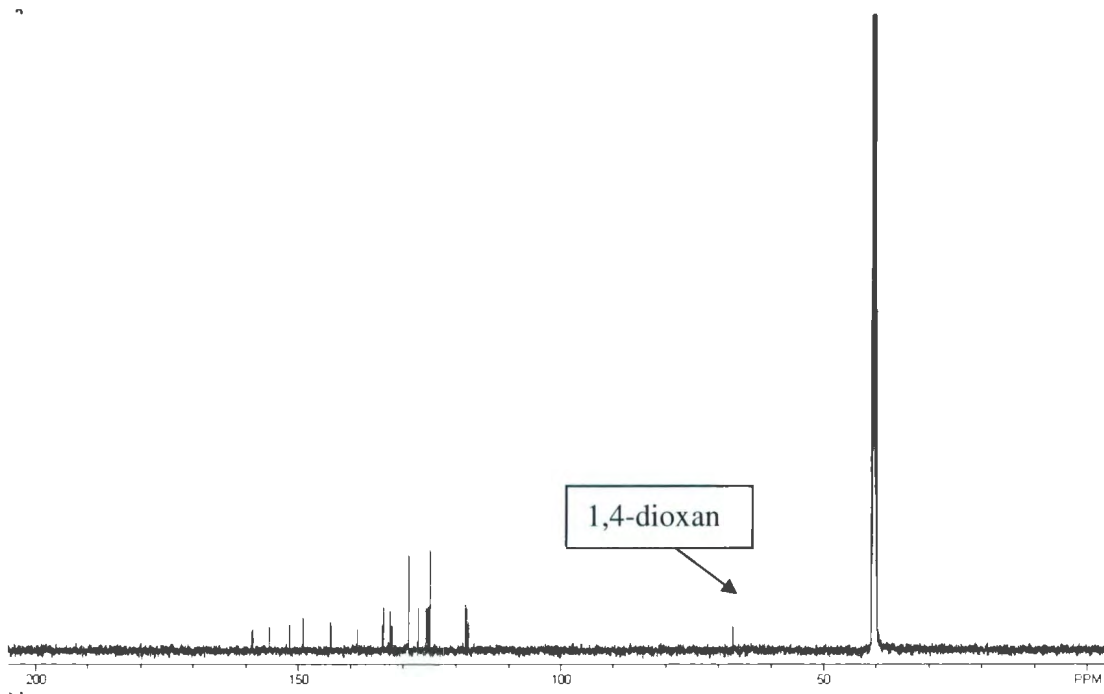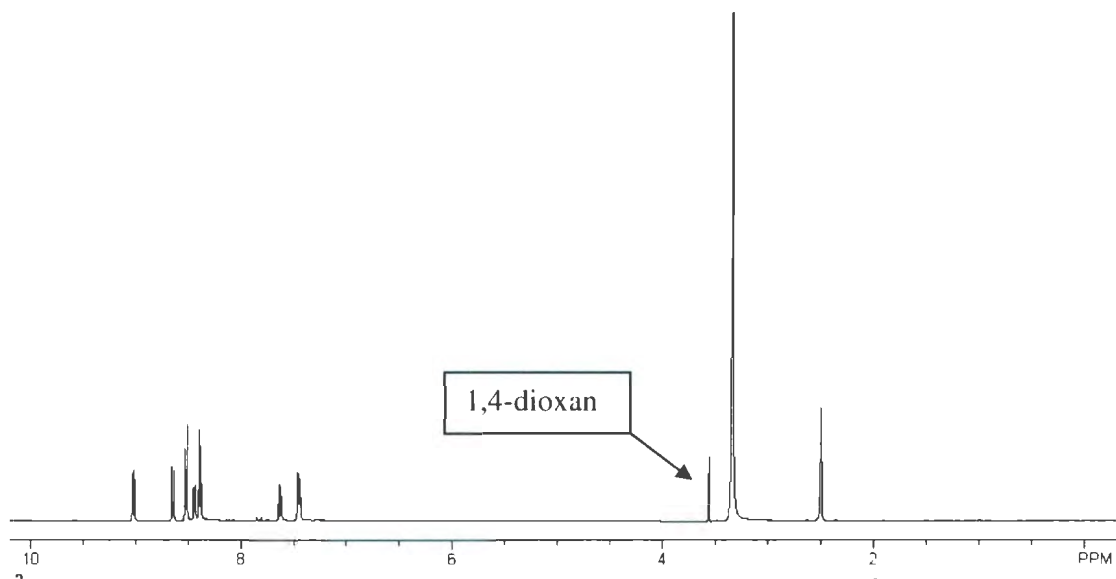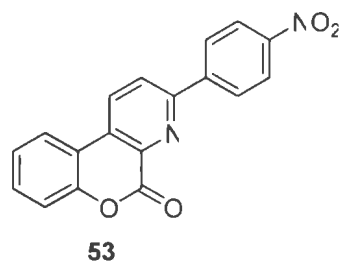
2.6.2 Assignment of Relative Stereochemistry

The key indicator that was used to assign the relative stereochemistry in the major diastereomer **24b** was the magnitude of coupling constant between H_{4a} and H_5. The large. coupling constant 11.5 Hz between H_{4a} and H_5 in the major diastereomer indicates a *trans*-diaxial relationship between these protons. As expected, no nOe was observed between these protons. However, an nOe was observed between H_{12c} and H_{4a} in both the isomers suggesting the *cis* arrangement of these protons (Fig. 2.3). In the minor diastereomer **24a**, H_{4a} and H_5 are *cis* to each other and consequently have an approximate gauche relationship. The coupling constant between these protons is accordingly low (2.1 Hz). Significant nOe effects (3.4%–5.7%) were observed between each of H_{12c}, H_{4a} and H_5 which is consistent with an all-*cis* arrangement of these protons. The enhancement observed between H_{12c} and H_5 is only possible via a 1,3-diaxial interaction. In the cases of *exo* diastereomer **24b**, the NMR-based assignments of the relative stereochemistry were corroborated by an X-ray crystal structure determination.
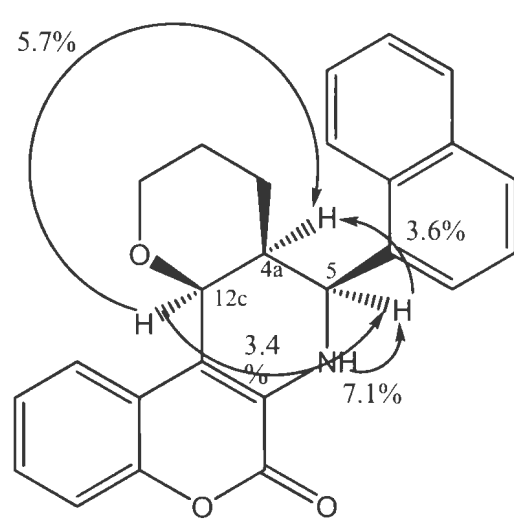
24a

J (H$_{4a}$-H$_5$) = 2.1 Hz
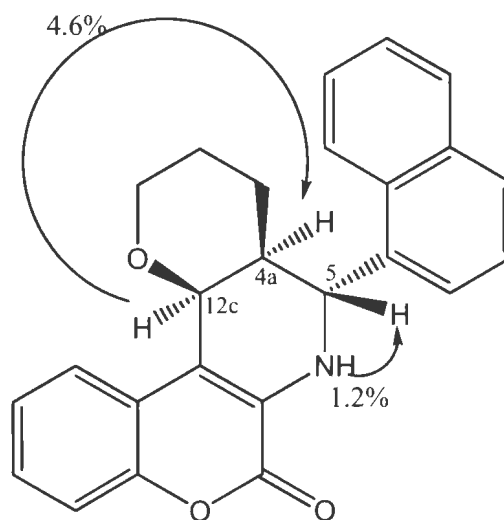
24b

J (H$_{4a}$-H$_5$) = 11.5 Hz

FIGURE 2.3. nOe studies on Povarov adducts

2.6.3 X-ray Crystal Structure Data for 24b

Data Collection

A colorless prism crystal of $C_{25}H_{21}NO_3$ having approximate dimensions of 0.35 x 0.20 x 0.10 mm was mounted on a glass fiber. All measurements were made on a Rigaku Saturn CCD area detector with graphite monochromated Mo-Kα radiation.

Indexing was performed from 330 images that were exposed for 12.0 seconds. The crystal-to-detector distance was 35.06 mm.

Cell constants and an orientation matrix for data collection corresponded to a primitive orthorhombic cell with dimensions:

$a = 8.3461(7)$ Å

$b = 18.8665(17)$ Å

$c = 23.936(2)$ Å

$V = 3769.0(6)$ Å^3

For $Z = 8$ and F.W. $= 383.45$, the calculated density is 1.351 g/cm^3. The systematic absences of:

h00: $h \pm 2n$

0k0: $k \pm 2n$

00l: $l \pm 2n$

uniquely determine the space group to be:

$P2_12_12_1$ (#19)

The data were collected at a temperature of $-120 \pm 1^{\circ}C$ to a maximum 2θ value of 61.8°. A total of 1140 oscillation images were collected. A sweep of data was done using ω scans from -50.0 to 70.0° in 0.5° step, at $\chi=0.0^{\circ}$ and $\phi = 0.0^{\circ}$. The exposure rate was 24.0 [sec./$^{\circ}$]. The detector swing angle was 10.09°. A second sweep was performed using ω scans from -80.0 to 85.0° in 0.5° step, at $\chi=54.0^{\circ}$ and $\phi = 90.0^{\circ}$. The exposure rate was 24.0 [sec./$^{\circ}$]. The detector swing angle was 10.09°. Another sweep was performed using ω scans from -50.0 to 70.0° in 0.5° step, at $\chi=0.0^{\circ}$ and $\phi = 90.0^{\circ}$. The exposure rate was 24.0 [sec./$^{\circ}$]. The detector swing angle was 10.09°. Another sweep was performed using ω scans from -80.0 to 85.0° in 0.5° step, at $\chi=54.0^{\circ}$ and $\phi = 180.0^{\circ}$. The exposure rate was 24.0 [sec./$^{\circ}$]. The detector swing angle was 10.09°. The crystal-to-detector distance was 35.06 mm. Readout was performed in the 0.137 mm pixel mode.

Data Reduction

Of the 63026 reflections that were collected, 7411 were unique ($R_{int} = 0.060$); equivalent reflections were merged. Data were collected and processed using CrystalClear (Rigaku). Net intensities and sigmas were derived as follows:

$$F^2 = [\Sigma(P_i - mB_{ave})] \cdot Lp^{-1}$$

where P_i is the value in counts of the ith pixel

m is the number of pixels in the integration area

B_{ave} is the background average

Lp is the Lorentz and polarization factor

$$B_{ave} = \Sigma(B_j)/n$$

where n is the number of pixels in the background area

B_j is the value of the jth pixel in counts

$$\sigma^2(F^2_{hkl}) = [(\Sigma P_i) + m((\Sigma(B_{ave} - B_j)^2)/(n-1))] \cdot Lp \cdot errmul + (erradd \cdot F^2)^2$$

where erradd = 0.00

errmul = 1.00

The linear absorption coefficient, μ, for Mo-Kα radiation is 0.885 cm^{-1}. A numerical absorption correction was applied which resulted in transmission factors ranging from 0.9805 to 0.9936. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction[2] was applied (coefficient = 0.006030).

Structure Solution and Refinement

The structure was solved by direct methods[3] and expanded using Fourier techniques[4]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement[5] on F^2 was based on 7411 observed reflections and 533 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma ||Fo| - |Fc|| / \Sigma |Fo| = 0.0588$$

$$wR2 = [\Sigma (w (Fo^2 - Fc^2)^2)/ \Sigma w(Fo^2)^2]^{1/2} = 0.1349$$

The standard deviation of an observation of unit weight[6] was 1.27. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.20 and -0.18 e$^-$/Å^3, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[7]. Anomalous dispersion effects were included in Fcalc[8]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[9]. The values for the mass attenuation coefficients are those of Creagh and Hubbell[10]. All calculations were performed using the CrystalStructure[11,12] crystallographic software package except for refinement, which was performed using SHELXL-97[3].

References

(1) CrystalClear: Rigaku Corporation, 1999. CrystalClear Software User's Guide, Molecular Structure Corporation, (c) 2000.J.W.Pflugrath (1999) Acta Cryst. D55, 1718-1725.

(2) Larson, A.C. (1970), Crystallographic Computing, 291-294. F.R. Ahmed, ed. Munksgaard, Copenhagen (equation 22, with V replaced by the cell volume).

(3) SHELX97: Sheldrick, G. M. (1997).

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

(5) Least Squares function minimized: (SHELXL97)

$$\Sigma w(F_o^2 - F_c^2)^2 \quad \text{where } w = \text{Least Squares weights.}$$

(6) 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

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

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

(9) 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).

(10) 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).

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

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

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{25}H_{21}NO_3$
Formula Weight	383.45
Crystal Color, Habit	colorless, prism
Crystal Dimensions	0.35 X 0.20 X 0.10 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Indexing Images	330 images @ 12.0 seconds
Detector Position	35.06 mm
Pixel Size	0.137 mm
Lattice Parameters	$a = 8.3461(7)$ Å
	$b = 18.8665(17)$ Å
	$c = 23.936(2)$ Å
	$V = 3769.0(6)$ Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	8
D_{calc}	1.351 g/cm^3
F_{000}	1616.00
μ(MoKα)	0.885 cm^{-1}

B. Intensity Measurements

Detector	Rigaku Saturn
Goniometer	Rigaku AFC8
Radiation	MoKα (λ = 0.71070 Å)
	graphite monochromated
Detector Aperture	70 mm x 70 mm
Data Images	1140 exposures
ω oscillation Range (χ=0.0, ϕ=0.0)	-50.0 - 70.0$^{\text{o}}$
Exposure Rate	24.0 sec./$^{\text{o}}$
Detector Swing Angle	10.09$^{\text{o}}$
ω oscillation Range (χ=54.0, ϕ=90.0)	-80.0 - 85.0$^{\text{o}}$
Exposure Rate	24.0 sec./$^{\text{o}}$
Detector Swing Angle	10.09$^{\text{o}}$
ω oscillation Range (χ=0.0, ϕ=90.0)	-50.0 - 70.0$^{\text{o}}$
Exposure Rate	24.0 sec./$^{\text{o}}$
Detector Swing Angle	10.09$^{\text{o}}$
ω oscillation Range (χ=54.0, ϕ=180.0)	-80.0 - 85.0$^{\text{o}}$
Exposure Rate	24.0 sec./$^{\text{o}}$
Detector Swing Angle	10.09$^{\text{o}}$
Detector Position	35.06 mm

Pixel Size	0.137 mm
$2\theta_{max}$	61.8°
No. of Reflections Measured	Total: 63026
	Unique: 7411 ($R_{int} = 0.060$)
Corrections	Absorption
	(trans factors: 0.9805 – 0.9936)
	Lorentz-polarization
	Secondary Extinction
	(coefficient: 6.03000e-003)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma\, w\, (F_o^2 - F_c^2)^2$
Least Squares Weights	$w = 1/[\,\sigma^2(F_o^2) + (0.0499 \cdot P)^2$
	$+\, 0.8919 \cdot P\,]$
	where $P = (Max(F_o^2, 0) + 2F_c^2)/3$
$2\theta_{max}$ cutoff	52.0^o
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	7411
No. Variables	533
Reflection/Parameter Ratio	13.90
Residuals: R1 ($I > 2.00\sigma(I)$)	0.0588
Residuals: R (All reflections)	0.0596
Residuals: wR2 (All reflections)	0.1349
Goodness of Fit Indicator	1.268
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	$0.20\ e^-/\text{Å}^3$
Minimum peak in Final Diff. Map	$-0.18\ e^-/\text{Å}^3$

TABLE 2.4 Bond lengths (Å)

atom	atom	distance	atom	atom	distance
O(1)	C(1)	1.395(3)	O(1)	C(9)	1.362(3)
O(2)	C(9)	1.213(3)	O(3)	C(10)	1.440(2)
O(3)	C(11)	1.438(3)	O(4)	C(26)	1.385(3)
O(4)	C(34)	1.363(3)	O(5)	C(34)	1.217(3)
O(6)	C(35)	1.441(3)	O(6)	C(36)	1.439(3)
N(1)	C(8)	1.378(3)	N(1)	C(15)	1.467(3)
N(2)	C(33)	1.383(3)	N(2)	C(40)	1.463(3)
C(1)	C(2)	1.388(3)	C(1)	C(6)	1.390(3)
C(2)	C(3)	1.375(4)	C(3)	C(4)	1.398(4)
C(4)	C(5)	1.387(3)	C(5)	C(6)	1.401(3)
C(6)	C(7)	1.452(3)	C(7)	C(8)	1.355(3)
C(7)	C(10)	1.507(3)	C(8)	C(9)	1.460(3)
C(10)	C(14)	1.536(3)	C(11)	C(12)	1.515(3)
C(12)	C(13)	1.524(4)	C(13)	C(14)	1.534(3)
C(14)	C(15)	1.532(3)	C(15)	C(16)	1.503(3)
C(16)	C(17)	1.366(3)	C(16)	C(25)	1.424(3)
C(17)	C(18)	1.425(3)	C(18)	C(19)	1.410(3)
C(18)	C(23)	1.420(3)	C(19)	C(20)	1.368(4)
C(20)	C(21)	1.409(4)	C(21)	C(22)	1.368(4)
C(22)	C(23)	1.416(3)	C(23)	C(24)	1.414(3)

C(24)	C(25)	1.370(3)	C(26)	C(27)	1.388(4)
C(26)	C(31)	1.393(3)	C(27)	C(28)	1.378(4)
C(28)	C(29)	1.387(4)	C(29)	C(30)	1.390(4)
C(30)	C(31)	1.406(3)	C(31)	C(32)	1.444(3)
C(32)	C(33)	1.360(3)	C(32)	C(35)	1.504(3)
C(33)	C(34)	1.456(3)	C(35)	C(39)	1.527(3)
C(36)	C(37)	1.506(4)	C(37)	C(38)	1.524(4)
C(38)	C(39)	1.535(3)	C(39)	C(40)	1.542(3)
C(40)	C(41)	1.509(3)	C(41)	C(42)	1.374(3)
C(41)	C(50)	1.418(3)	C(42)	C(43)	1.416(3)
C(43)	C(44)	1.417(3)	C(43)	C(48)	1.418(3)
C(44)	C(45)	1.366(4)	C(45)	C(46)	1.399(4)
C(46)	C(47)	1.370(4)	C(47)	C(48)	1.426(3)
C(48)	C(49)	1.416(3)	C(49)	C(50)	1.362(3)

TABLE 2.5 Bond angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
C(1)	O(1)	C(9)	121.7(2)	C(10)	O(3)	C(11)	
	111.74(18)						
C(26)	O(4)	C(34)	121.9(2)	C(35)	O(6)	C(36)	
	111.4(2)						
C(8)	N(1)	C(15)	117.3(2)	C(33)	N(2)	C(40)	
	116.8(2)						
O(1)	C(1)	C(2)	115.8(2)	O(1)	C(1)	C(6)	
	120.7(2)						
C(2)	C(1)	C(6)	123.5(2)	C(1)	C(2)	C(3)	
	118.5(2)						
C(2)	C(3)	C(4)	120.3(2)	C(3)	C(4)	C(5)	
	120.0(2)						
C(4)	C(5)	C(6)	121.2(2)	C(1)	C(6)	C(5)	
	116.5(2)						
C(1)	C(6)	C(7)	119.4(2)	C(5)	C(6)	C(7)	
	124.1(2)						
C(6)	C(7)	C(8)	118.3(2)	C(6)	C(7)	C(10)	
	122.3(2)						

C(8)	C(7)	C(10)	119.5(2)	N(1)	C(8)	C(7)
	124.2(2)					
N(1)	C(8)	C(9)	113.6(2)	C(7)	C(8)	C(9)
	122.2(2)					
O(1)	C(9)	O(2)	118.4(2)	O(1)	C(9)	C(8)
	117.6(2)					
O(2)	C(9)	C(8)	123.9(2)	O(3)	C(10)	C(7)
	106.10(18)					
O(3)	C(10)	C(14)	111.10(19)	C(7)	C(10)	C(14)
	111.8(2)					
O(3)	C(11)	C(12)	111.5(2)	C(11)	C(12)	C(13)
	109.7(2)					
C(12)	C(13)	C(14)	111.3(2)	C(10)	C(14)	C(13)
	110.0(2)					
C(10)	C(14)	C(15)	109.01(19)	C(13)	C(14)	C(15)
	113.3(2)					
N(1)	C(15)	C(14)	107.60(19)	N(1)	C(15)	C(16)
	109.3(2)					
C(14)	C(15)	C(16)	115.7(2)	C(15)	C(16)	C(17)
	120.6(2)					
C(15)	C(16)	C(25)	120.7(2)	C(17)	C(16)	C(25)
	118.6(2)					

C(16)	C(17)	C(18)	122.0(2)	C(17)	C(18)	C(19)
			121.7(2)			
C(17)	C(18)	C(23)	118.7(2)	C(19)	C(18)	C(23)
			119.6(2)			
C(18)	C(19)	C(20)	120.4(2)	C(19)	C(20)	C(21)
			120.6(2)			
C(20)	C(21)	C(22)	120.0(2)	C(21)	C(22)	C(23)
			121.1(2)			
C(18)	C(23)	C(22)	118.4(2)	C(18)	C(23)	C(24)
			118.5(2)			
C(22)	C(23)	C(24)	123.0(2)	C(23)	C(24)	C(25)
			121.3(2)			
C(16)	C(25)	C(24)	120.8(2)	O(4)	C(26)	C(27)
			116.4(2)			
O(4)	C(26)	C(31)	120.8(2)	C(27)	C(26)	C(31)
			122.8(2)			
C(26)	C(27)	C(28)	118.7(2)	C(27)	C(28)	C(29)
			120.4(2)			
C(28)	C(29)	C(30)	120.4(2)	C(29)	C(30)	C(31)
			120.4(2)			
C(26)	C(31)	C(30)	117.2(2)	C(26)	C(31)	C(32)
			118.8(2)			

C(30)	C(31)	C(32)	123.9(2)	C(31)	C(32)	C(33)
			119.3(2)			
C(31)	C(32)	C(35)	120.5(2)	C(33)	C(32)	C(35)
			120.0(2)			
N(2)	C(33)	C(32)	123.6(2)	N(2)	C(33)	C(34)
			115.2(2)			
C(32)	C(33)	C(34)	121.2(2)	O(4)	C(34)	O(5)
			118.2(2)			
O(4)	C(34)	C(33)	117.9(2)	O(5)	C(34)	C(33)
			123.8(2)			
O(6)	C(35)	C(32)	105.1(2)	O(6)	C(35)	C(39)
			112.1(2)			
C(32)	C(35)	C(39)	112.3(2)	O(6)	C(36)	C(37)
			110.5(2)			
C(36)	C(37)	C(38)	109.3(2)	C(37)	C(38)	C(39)
			111.0(2)			
C(35)	C(39)	C(38)	110.4(2)	C(35)	C(39)	C(40)
			110.5(2)			
C(38)	C(39)	C(40)	113.5(2)	N(2)	C(40)	C(39)
			107.0(2)			
N(2)	C(40)	C(41)	111.2(2)	C(39)	C(40)	C(41)
			112.2(2)			

C(40)	C(41)	C(42)	120.2(2)	C(40)	C(41)	C(50)
	121.0(2)					
C(42)	C(41)	C(50)	118.8(2)	C(41)	C(42)	C(43)
	121.8(2)					
C(42)	C(43)	C(44)	122.4(2)	C(42)	C(43)	C(48)
	118.9(2)					
C(44)	C(43)	C(48)	118.6(2)	C(43)	C(44)	C(45)
	121.1(2)					
C(44)	C(45)	C(46)	120.2(2)	C(45)	C(46)	C(47)
	120.9(2)					
C(46)	C(47)	C(48)	120.1(2)	C(43)	C(48)	C(47)
	119.0(2)					
C(43)	C(48)	C(49)	118.3(2)	C(47)	C(48)	C(49)
	122.7(2)					
C(48)	C(49)	C(50)	121.5(2)	C(41)	C(50)	C(49)
	120.7(2)					

Chapter 3. Intramolecular Inverse Electron Demand Diels-Alder (IEDDA) Reactions of Coumarin-fused 2-Azadienes

3.1 Introduction

A large number of biologically active natural products and drugs have polycyclic structures. The synthesis of such systems usually requires at least one key cyclization event, which is often accompanied by the generation of one or more stereogenic centers.[1] In most cases, cyclization is a key step in the synthesis of such molecules, especially if the molecule is chiral. Therefore, predictable control over the regio- and stereoselectivity of the cyclization step is of paramount importance. As is evident from numerous examples in the literature,[2] the Diels-Alder reaction can be performed predictably with high levels of regio- and stereochemical control. Further advantages are its very broad scope and functional group tolerance.

Logically, if the reacting partners of a Diels-Alder reaction, *i.e.* a diene and a dienophile, are constrained to be in a single molecule by a tether, the Diels-Alder reaction allows the formation of more than one ring in a single step. This variant of the Diels-Alder reaction is termed as the intramolecular Diels-Alder (IMDA) reaction. As shown in Scheme 3.1, compounds having various polycyclic skeleta can potentially be accessed *via* the IMDA reaction.

SCHEME 3.1 Synthesis of Polycyclic Structures *via* the IMDA Reaction
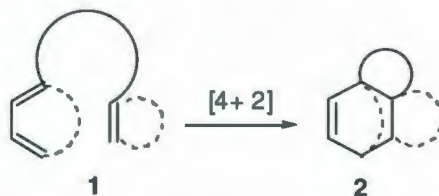
Few other methods provide such rapid access to these kinds of polycyclic structures.[3] Depending upon the structural constraints, enhanced (or reversed) regio- and stereoselectivity can be expected in the IMDA reaction.[4] Also, the IMDA reaction, like any other intramolecular reaction, benefits from an entropic advantage as compared to the corresponding intermolecular reaction and thus can often be performed under milder reaction conditions.

The first example of an intramolecular Diels-Alder reaction appears to be an unpublished result quoted by Alder and Schumacher in 1953,[4] in which 1,4-pentadiene (**3**) and dimethylacetylenedicarboxylate (**4**) were reported to afford bicyclo[4.1.0]heptane derivative **6**, *via* an *in situ*-generated ene adduct **5** (Scheme 3.2). In the beginning of the early 1960s, some isolated examples of IMDA reactions were published.[5] However, it was not until the reports by Brieger (attempted synthesis of longifolene **9**) (Scheme 3.3),[6] Klemm (synthesis of γ-apopicropodophyllin **16**) (Scheme 3.4)[7] and Oppolzer (synthesis of chelidonine **20**) (Scheme 3.5)[8] that the IMDA reaction started to gain a more prominent place in the field of synthesis. Since then, many spectacular examples of the application of the IMDA reaction to complex synthetic targets have been documented.[9] A particularly impressive example is Shair's dual Diels-Alder-based strategy during the synthesis (−)-longithorone A.[9c]

SCHEME 3.2 The First IMDA Reaction
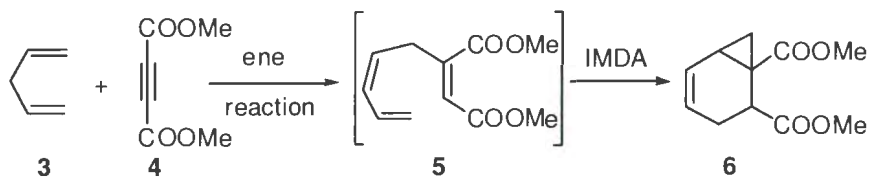
SCHEME 3.3 Attempted Synthesis of Longifolene (9) by Brieger
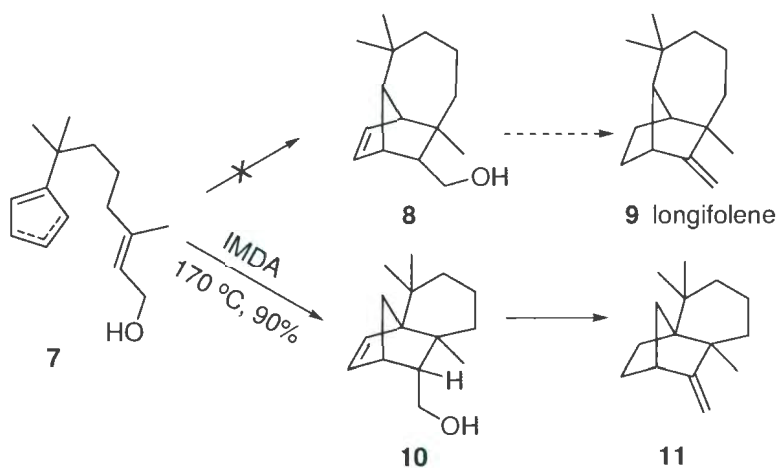
In Chapter 2, the Povarov reactions of a series of *in situ*-generated coumarin-fused 2-azadienes were described. The key step of these Povarov reactions is an IEDDA reaction. In its one-pot version (multi-component reaction), this reaction affords tri- or tetrayclic heterocycles. The possibility of extending this to an intramolecular variant was attractive due to the potential of forming structurally more complex products in one operation.

SCHEME 3.4 Total Synthesis of *rac*-γ-Apopicropodophyllin (**16**) by Klemm *et al.*
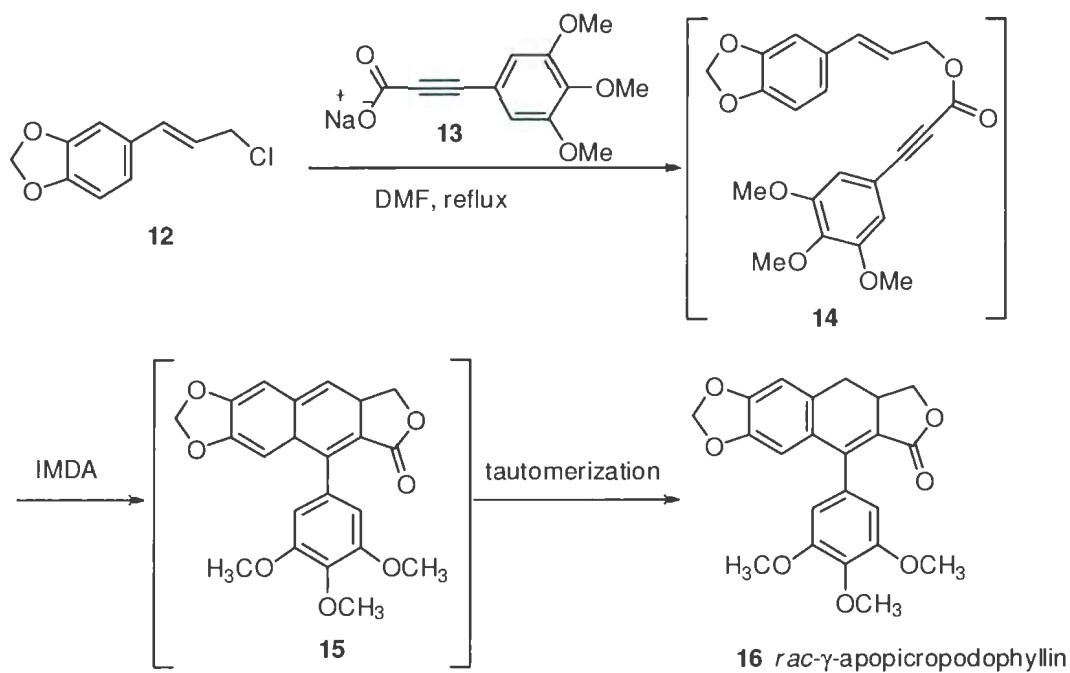
SCHEME 3.5 Total Synthesis of *dl*-Chelidonine (**20**) by Oppolzer *et al.*
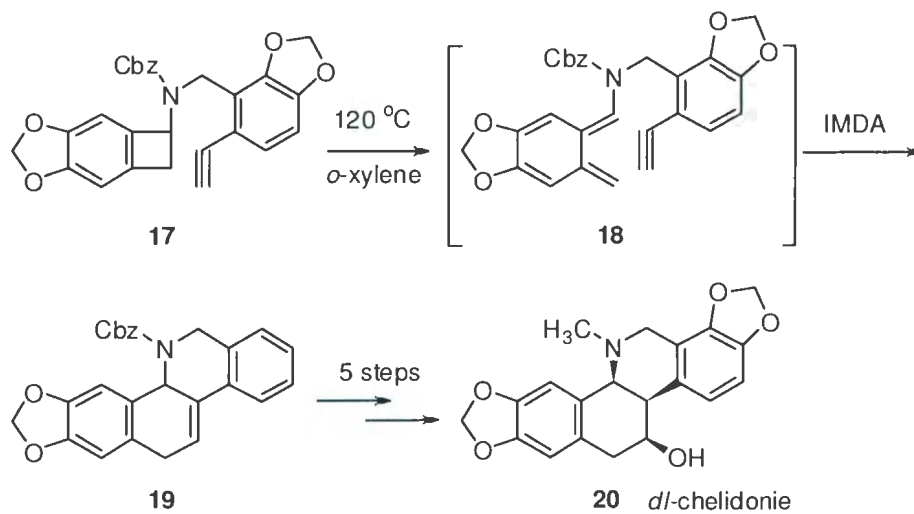
3.2 Results and Discussion

3.2.1 Type 1 and Type 2 IMDA Reactions

There are two ways to connect a diene and a dienophile for an IMDA reaction.[12] When the diene and dienophile are connected at a terminal position of the diene (C-1 or C-4), a fused bicyclic (or polycyclic) compound is usually the product. This type of IMDA is called a Type 1 IMDA reaction. On the other hand, if the diene and dienophile are connected through C-2 or C-3 of the diene, bridged bicyclic ring systems are formed (Scheme 3.6). This variant is referred to as a Type 2 IMDA reaction.[12] For the study of IMDA reactions of coumarin-fused 2-azadienes, attention was focused exclusively on Type 1 IMDA reactions.

SCHEME 3.6 Type 1 and Type 2 IMDA Reactions
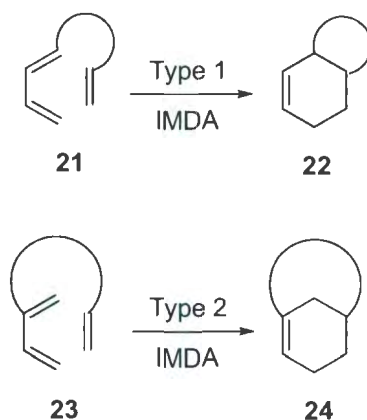
3.2.2 Exploratory Studies on Intramolecular Povarov Reactions

Based on the previous findings (Chapter 2) that 3-aminocoumarin (**25**) condenses with aromatic aldehydes *in situ* and the resulting 2-azadienes undergo a Povarov reaction

in the presence of an electron rich alkene and catalytic amount of Yb(OTf)$_3$, it was envisioned that aldehyde derivatives of the general structure **26** might give rise to intramolecular Povarov reactions upon reaction with 3-aminocoumarin (**25**) to afford pentacyclic products **28** (Scheme 3.7).

SCHEME 3.7 Povarov Reaction between 3-Aminocoumarin (**25**) and Aldehyde **26**

Having a Pendant Dienophile
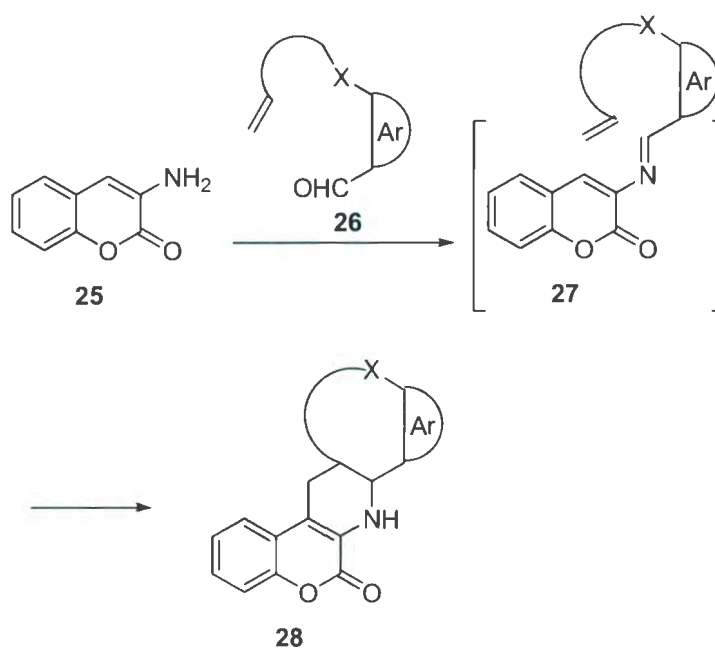
For initial studies, 2-(allyloxy)benzaldehyde (**29**),[13] which was prepared in 87% yield by the *O*-alkylation of salicylaldehyde with allyl bromide in the presence of anhydrous K$_2$CO$_3$, was chosen. Enal **29** was then reacted with 3-aminocoumarin (**25**) in the presence of 5 mol% Yb(OTf)$_3$. No reaction was evident at room temperature (tlc analysis). This was not surprising because the C=C bond in the allyl group is electron

neutral and would therefore not be expected to easily take part in an IEDDA reaction, even an intramolecular one. However, upon heating for 19 hours at reflux, three new products were isolated along with 23% recovery of 3-aminocoumarin (**25**) (Scheme 3.8).

SCHEME 3.8 Reaction of 3-Aminocoumarin (**25**) with 2-(Allyloxy)benzaldehyde (**29**)
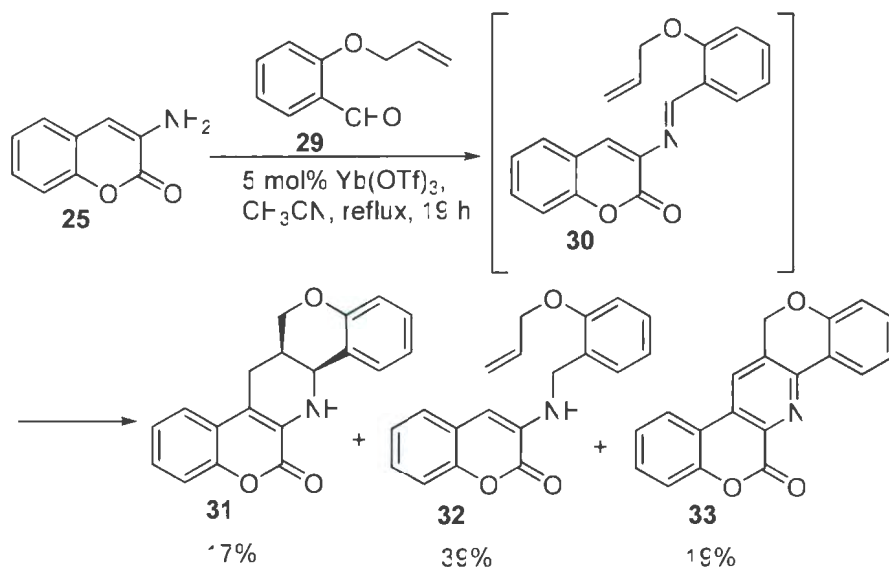
One of these new products was determined to be the Povarov adduct **31**, which is the product of an *endo* transition state in the (formal) IEDDA step of the Povarov reaction. The relative stereochemistry of **31** was established based on its 1D and 2D NMR spectra. In the ^{1}H NMR spectrum, H-7a appeared as a singlet (instead of a doublet), presumably due to a very small coupling constant with the *cis* proton H-13a. The other two products were assigned to structures **32** and **33**. Compound **33** is an oxidized (dehydrogenated) version of **31** while **32** is a reduced form of the *in situ*-generated imine **30**. This suggested that these two products were formed as a result of

transfer hydrogenation from Povarov adduct **31** to the *in situ*-generated imine **30**. The observed ratio of 2:1 for the yields of **32** and **33** is consistent with this notion. Interestingly, such transfer hydrogenations during Povarov reactions of aniline-derived azadienes were reported very recently.[14] Although the Povarov adduct was isolated in only 17% yield, this result was encouraging, especially considering that the double bond in the allyl group is not a very good dienophile for the IEDDA reaction.

On the basis of the above finding, it was anticipated that the employment of an alkyne-containing side chain as a dienophile for the intramolecular IEDDA reaction would more easily afford **33** because the Povarov adduct would only need to lose two hydrogen atoms to form the aromatized product. In this vein, 2-(propargyloxy)benzaldehyde (**34**)[15] was reacted with 3-aminocoumarin (**25**). Very slow progress of the reaction was observed (tlc analysis). 3-Aminocoumarin (**25**) was recovered (19%) after heating the reaction mixture in acetonitrile for 9 days. Nevertheless, the aromatized product **33** was isolated in 47% yield (Scheme 3.9). As anticipated, the aromatized product **33** was isolated in a better yield (47%) as compared to the first reaction involving an allylic double bond as a dienophile. However, no reduced product corresponding to **32** was isolated, which may indicate that the oxidation of **36** occurs by some other mechanism.

The slow rate of this reaction may be also attributed to the electron neutral nature of the dienophile. Of course, IEDDA reactions proceed more easily with electron rich dienophiles. Thus, it was speculated that the activation of the alkynic dienophile by the introduction of a phenyl group at the terminal position of the dienophile might result in a

SCHEME 3.9 Intramolecular Povarov Reaction between **25** and **34**
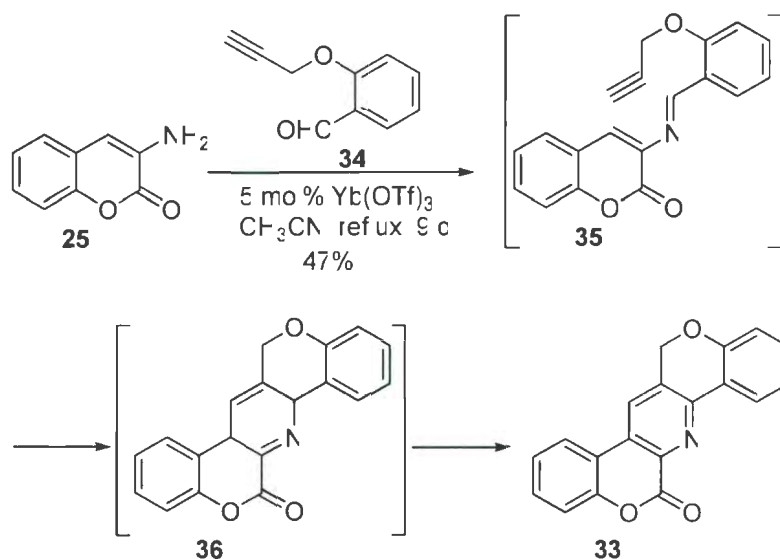
faster reaction. In this vein, an aldehyde **42** having an alkyne-containing side chain was synthesized (Scheme 3.10). The synthesis of this aldehyde commenced with a Sonogashira reaction between bromobenzene (**37**) and propargyl alcohol (**38**) to afford compound **39** in 73% yield.[16] Ynol **39** was then converted into bromide **40** upon treatment with CBr$_4$/PPh$_3$.[17] The crude bromide was used for the next step without purification. O-Alkylation of salicylaldehyde (**41**) with crude bromide **40** smoothly afforded aldehyde **42**[18] in 72% yield (over 2 steps).

No reaction was observed at room temperature when aldehyde **42** was stirred with 3-aminocoumarin (**25**) in the presence of 10 mol% Yb(OTf)$_3$ for 3 hours. However, heating **42** and **25** at reflux, resulted in the formation of a new product (tlc analysis). The reaction was stopped after 48 hours of reflux. Although the starting materials **25** and **42** had not been fully consumed, tlc analysis indicated that byproducts were becoming more

abundant. The aromatized product **43** was isolated in 43% yield by column chromatography along with 27% of the starting material 3-aminocoumarin (**25**) (Scheme 3.10).

SCHEME 3.10 Intramolecular Povarov Reaction between **42** and **25**
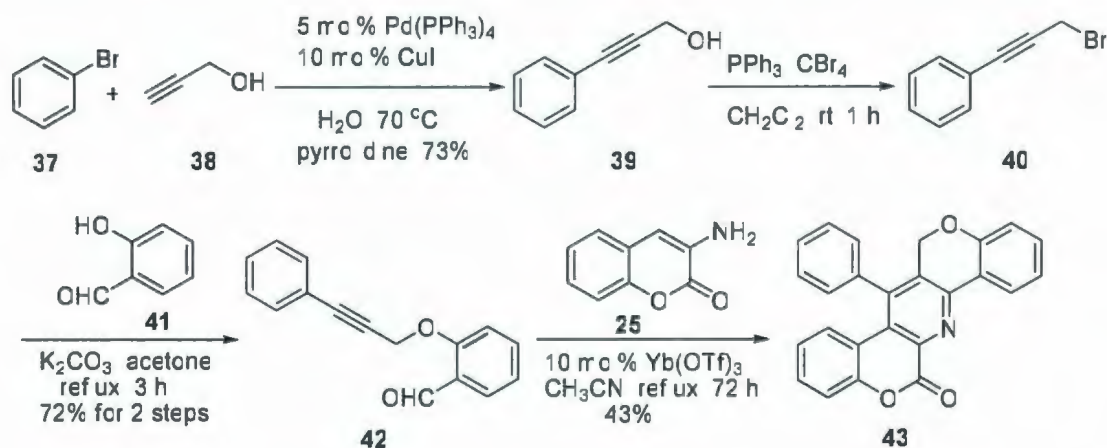
During the investigations on the intermolecular Povarov reactions, styrenes were found to react with the preformed coumarin-fused 2-azadienes at room temperature with good/satisfactory levels of *endo/exo* selectivity.[19] This prompted the investigation of styrene derivatives in the intramolecular version of the reaction. In this vein, 2-(cinnamyloxy)benzaldehyde (**45**) was prepared by the *O*-alkylation of salicylaldehyde (**41**) with cinnamyl bromide **44**.[20]

When 2-(cinnamyloxy)benzaldehyde (**45**) was reacted with 3-aminocoumarin (**44**) in the presence of 5 mol% Yb(OTf)₃ in acetonitrile, the *exo* diastereomer of the Povarov adduct **46** was formed in 56% yield (Scheme 3.11). More interestingly, this reaction proceeded at room temperature in 1 hour. The yield could be improved to 85%

by using 10 mol% catalyst. In an analogous fashion to that of the intermolecular Povarov adducts (Chapter 2), the relative stereochemistry of **46** was assigned based on standard 1D and 2D NMR experiments. The magnitude of the coupling constants between H_{7a}-H_{13a} (11.1 Hz) and H_{14}-H_{13a} (11.0 Hz) were used as key indicators of the relative stereochemistry.

SCHEME 3.11 Povarov Reaction between **45** and **25**
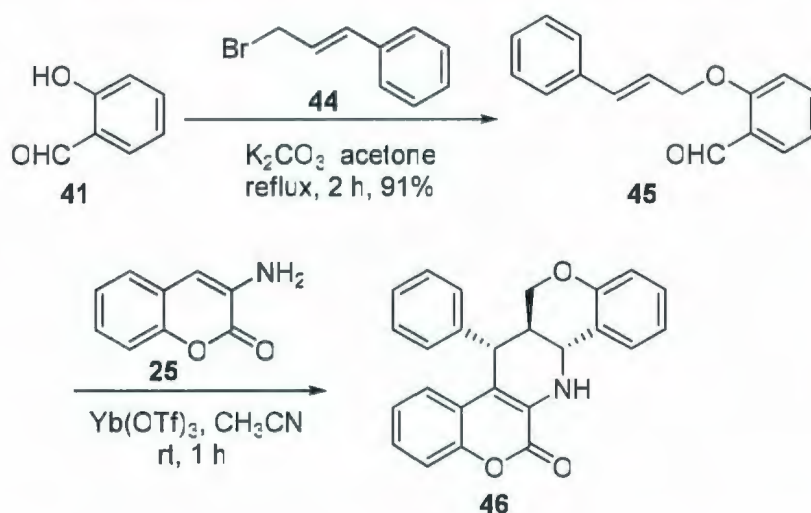
Traces of what appears to be the other diastereomer (*endo*) could be detected in the ^{1}H NMR of the crude reaction mixture. However, attempts to isolate it by flash chromatography failed. This reaction also had the practical advantage that the major Povarov adduct (*exo* diastereomer) precipitated as the reaction progressed. Therefore, the product could be isolated by simple suction filtration of the reaction mixture after the starting 3-aminocoumarin (**25**) was totally consumed (tlc analysis).

It was envisaged at this stage that the application of 2-formylphenyl cinnamate

(**48**) in the intramolecular Povarov reaction with 3-aminocoumarin (**25**) would result in the formation of a product that would contain a new dihydrocoumarin moiety (Scheme 3.12). Therefore, 2-formylphenyl cinnamate (**48**) was prepared (90%) from salicylaldehyde (**41**) and *trans*-cinnamic acid (**47**) using slightly modified literature conditions.[21]

As anticipated for an electron deficient dienophile, the reaction of 2-formylphenyl cinnamate (**48**) with 3-aminocoumarin (**25**) did not show any signs of progress at room temperature. After heating the reaction mixture at reflux for 60 hours, some conversion was observed (by tlc analysis) and a white solid was obtained by suction filtration of the crude reaction mixture. The ^{1}H NMR spectrum of this product was complicated due to the apparent presence of more than one compound. Nevertheless, it clearly showed the presence of signals corresponding to the expected *exo* Povarov adduct **49**. The characteristic signals in the ^{1}H NMR spectrum were 5.56 (s, 1H), 4.99 (d, J = 10.0 Hz, 1H), 4.45 (d, J = 10.9 Hz, 1H) and 3.18 (m, 1H). This white product was insoluble in common organic solvents and hence could not be purified. LC/MS analysis of this product showed a molecular ion peak (m/z = 395) corresponding to the expected Povarov adduct **49**.

SCHEME 3.12 Attempted Intramolecular Povarov Reaction between **48** and **25**
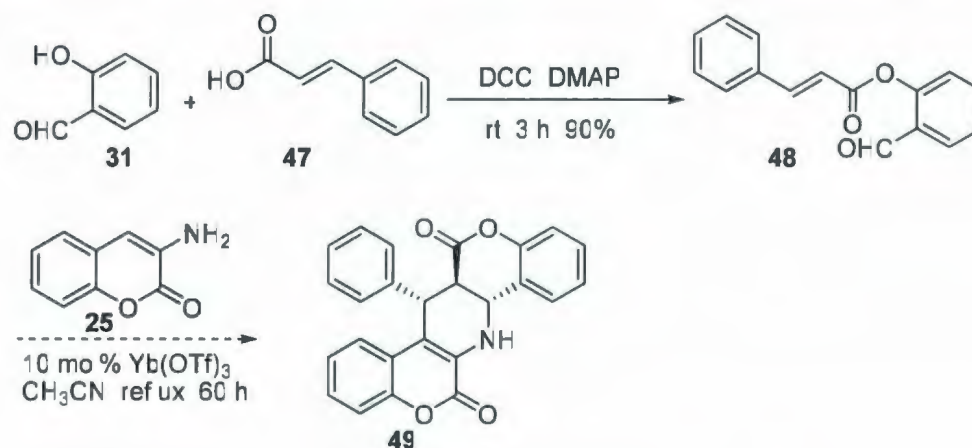
The introduction of electron donating substituents on the phenyl ring in the cinnamoyl unit would be expected to assist the participation of this dienophile in the Povarov reaction and possibly enhance the solubility of the product. Therefore, 2,3-dimethoxycinnamic acid (**50**)[22] was converted into its salicylyl ester (**51**) upon reaction with salicylaldehyde (**41**) in the presence of DCC and DMAP. However, ester formation was very slow. No reaction was evident at room temperature for 2 hours. The starting materials were not totally consumed (tlc analysis) even after heating the reaction mixture for 28 hours at reflux. Only 18% yield of the desired product **51** was achieved along with the 61% recovery of salicylaldehyde (**41**). This result is not surprising, considering that the lone pairs of the *ortho*-situated methoxy group are conjugated with the carbonyl group, which attenuates its electrophilicity. Nevertheless, a sufficient quantity of the ester **51** was obtained for subsequent study (Scheme 3.13).

Disappointingly, however, the presence of the methoxy groups did not appear to have any beneficial effect on the attempted Povarov reaction. The reaction again did not

show any signs of progress at room temperature. After heating at reflux for 72 hours, traces of a new product were observed (tlc analysis). Steric crowding due to the two methoxy groups may also account for the poor reactivity of this dienophile. The insoluble white product was isolated by suction filtration and it showed a molecular ion peak (m/z = 455) and signals in the ^{1}H NMR spectrum {4.75 (d, J = 10.0 Hz), 4.44 (d, J = 10.0 Hz and 3.39 (br, m)} that are consistent with the Povarov adduct **52**. However, due to solubility problems, this product could not be isolated in a pure form.

SCHEME 3.13 Attempted Intramolecular Povarov Reaction between **51** and **25**
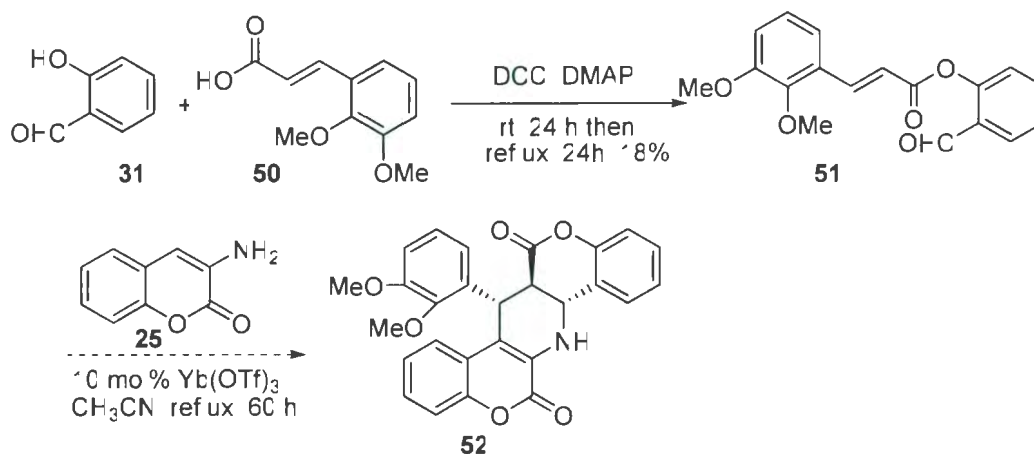
3.2.3 Scope of Intramolecular Povarov Reactions

The reaction between 3-aminocoumarin (**25**) and 2-(cinnamyloxy)benzaldehyde (**45**) offers three points of diversity, *i.e.* the carbocyclic ring of the coumarin unit, the aromatic ring of the aldehyde unit that connects the dienophile to diene and the dienophile. Thus, a small library of pentacyclic heterocycles could potentially be formed

by a simple sequence of reactions. In order to make progress toward this objective, a variety of 3-aminocoumarins with different substituents on the carbocyclic ring of coumarin were required. Also, a set of cinnamyl bromides for reactions with various salicylaldehyde derivatives was desired to form the dienophile-tethered aromatic aldehydes.

Although commercially available, the parent cinnamyl bromide (44) could be prepared from less expensive cinnamyl alcohol,[23] which, in turn, could be obtained easily from ethyl cinnamate upon reduction with DIBAL-H. Similarly, other cinnamyl bromides (Ar = 4-bromophenyl[24] and 4-nitrophenyl[25]) were prepared from the corresponding aldehydes 53 and 54 in three steps using the published methods.[24,25] Salicylaldehyde (41) was O-alkylated upon reaction with the cinnamyl bromides 53 and 54 in the presence of anhydrous K_2CO_3 in refluxing acetone in good yields (81% and 67%, respectively) (Scheme 3.14).

SCHEME 3.14 Synthesis of 2-(Cinnamyloxy)benzaldehydes 55 and 56

53 Ar = 4-BrC$_6$H$_4$

54 Ar = 4-(NO$_2$)C$_6$H$_4$

55 Ar = 4-BrC$_6$H$_4$, R$_1$ = H, 81%

56 Ar = 4-(NO$_2$)C$_6$H$_4$, R$_1$ = H, 67%
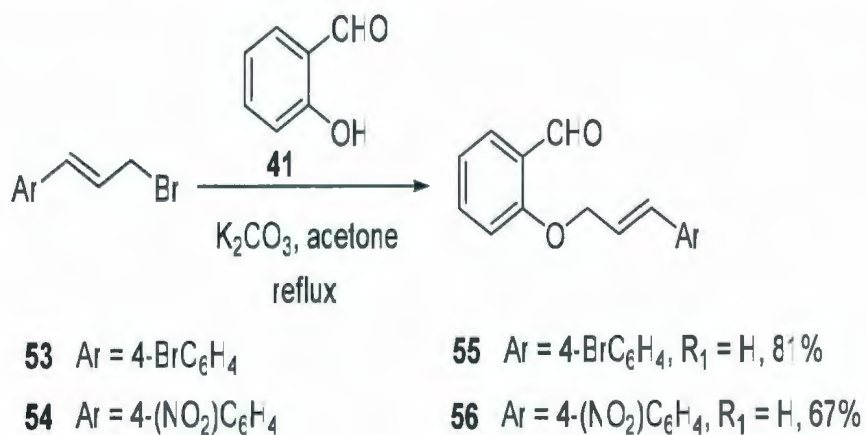
As with the reaction involving aldehyde **45** (Scheme 3.11), the reaction between 3-aminocoumarin (**25**) and aldehyde **55** proceeded smoothly at room temperature. A precipitate formed immediately after the addition of Yb(OTf)₃ to a solution of 3-aminocoumarin (**25**) and aldehyde **55** (R = Br). After 2 hours of reaction, the precipitate was isolated by suction filtration in 84% yield and determined to be the *exo* diastereomer **57** arising from an intramolecular IEDDA reaction (Scheme 3.15). The ¹H NMR spectrum of the filtrate did not show the presence of any signals expected for the *endo* diastereomer. The reaction took 2 hours for complete consumption of 3-aminocoumarin (**25**), whereas the parent reaction (R = H) was complete after 1 hour at room temperature. The slightly longer reaction time can be attributed to the –*I* effect of the bromo group in 4-position of the phenyl ring, which would be expected to destabilize any developing positive charge at the benzylic carbon at the transition state.

SCHEME 3.15 Intramolecular Povarov Reaction between **25** and **55**
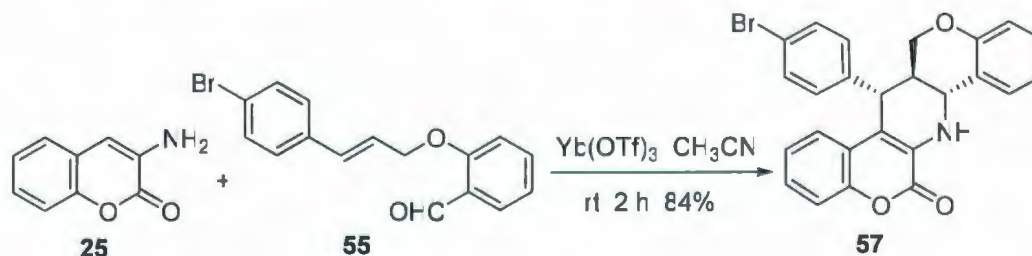
Based on this result, it was anticipated that the aldehyde **56** (R = NO₂), if subjected to similar reaction conditions, would take a much longer time for the reaction to run to completion. Indeed, this reaction took 5 days at room temperature for the complete consumption of the starting 3-aminocoumarin (**25**). The fact that this reaction

occurs at all at room temperature is a testament to the power of the IMDA reaction. Again, only the *exo* diastereomer **58** was isolated (Scheme 3.16). A single crystal X-ray structure determination for **58** confirmed that the NMR-based assignments of the relative stereochemistry were correct (Fig. 3.2). Traces of what appeared to be the *endo* diastereomer were observed in ^{1}H NMR spectrum of the crude reaction mixture, but this product could not be isolated by flash chromatography.

SCHEME 3.16 Intramolecular Povarov Reaction between **25** and **56**
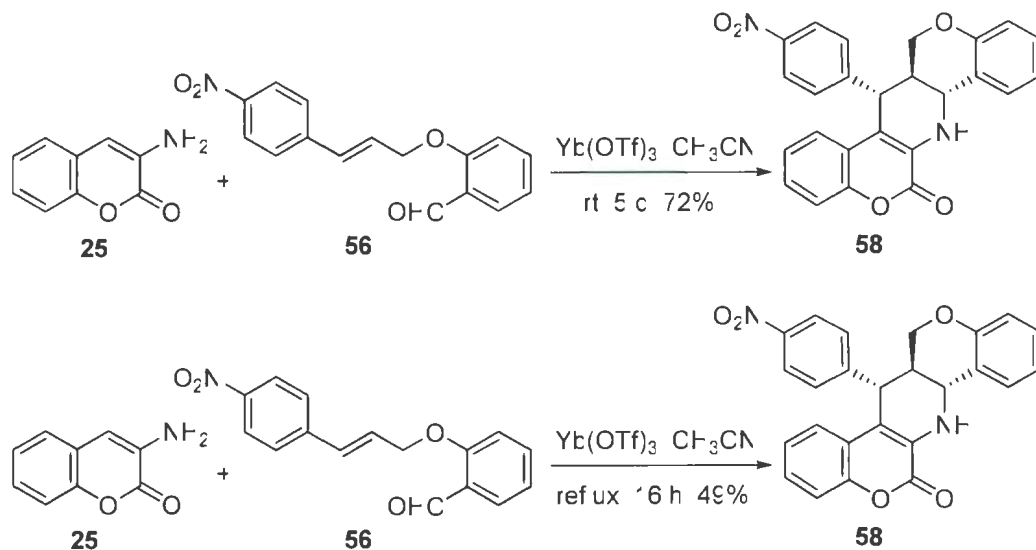
When the reaction was repeated at reflux in acetonitrile, the reaction was complete after 16 hours (Scheme 3.16). However, a lower yield (49%) of the *exo* diastereomer was obtained and a complex mixture of other products formed. Having already prepared a variety of 3-aminocoumarins (Chapter 1), these compounds were then employed in the intramolecular Povarov reactions with various 2-

(cinnamyloxy)benzaldehyde derivatives. The parent 2-(cinnamyloxy)benzaldehyde (**45**) was chosen for the initial set of reactions. All of the reactions proceeded smoothly at room temperature to afford the corresponding *exo* diastereomers in good yields (78-87%) and excellent diastereoselectivity (<5:>95) (Table 3.1).
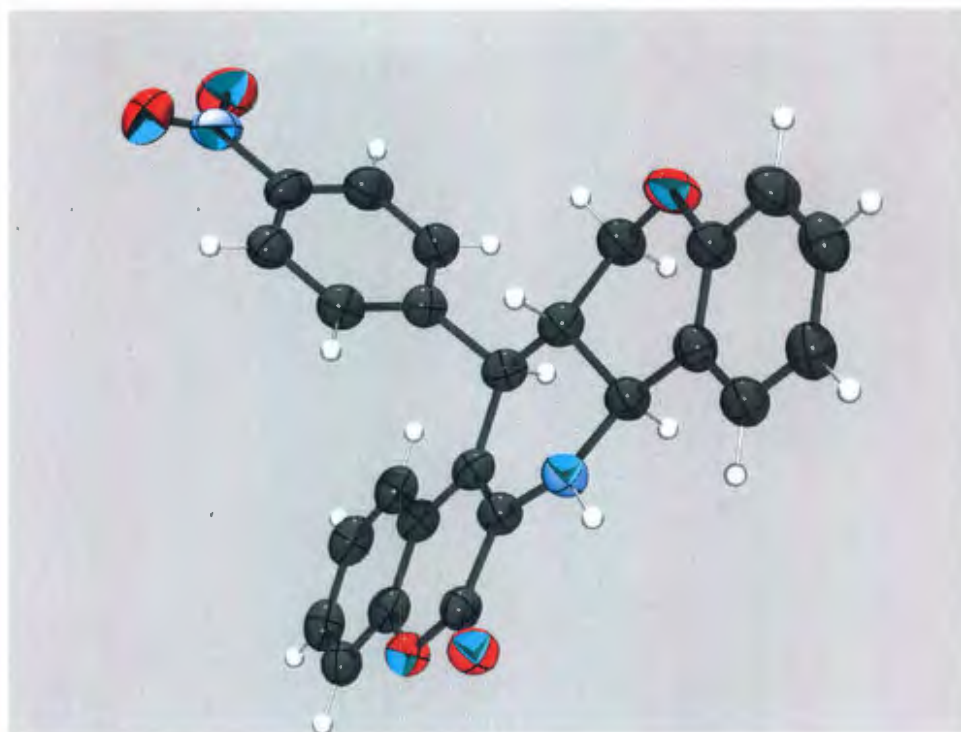
FIGURE 3.1 Pov-ray Representation of **58**

TABLE 3.1 Intramolecular Povarov Reactions between **59** and **45**
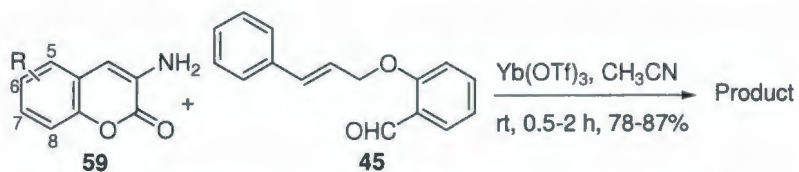
Entry	R	Product	Yield[a,b]
1	6-CH₃	**60**	87
2	6-OCH₃	**61**	84[c]
3	6-Br	**63**	78
4	6-NO₂	**64**	82
5	8-OCH₃	**65**	86

[a] *endo/exo* ratio <5:95, determined by ¹H NMR analysis of the crude mixtures. [b] Isolated yields.
[c] Additionally, **62** was isolated in 2% yield.
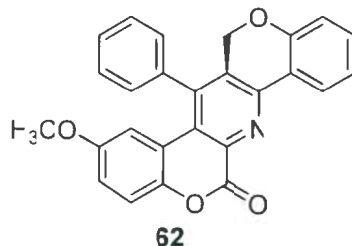
FIGURE 3.2 Side product **62** from Intramolecular Povarov Reaction between **59** (R = 6-

OMe) and **45**

All of these reactions had the practical advantage that the *exo* diastereomer has

low solubility in acetonitrile. Only on one occasion were small amounts of two minor

products isolated by flash chromatography of the filtrate (Entry 2, Table 3.1) in small

quantities. One of these products was an isomer of **53** (by LC/MS analysis), presumably

the product arising from an *endo* transition state. The ^{1}H NMR and mass spectra of the

other product showed signals consistent with the aromatized product **62**. This product

was isolated in 2% yield (Figure 3.2). It was characterized by ^{1}H NMR spectrum, IR and

mass spectrometry. ^{13}C NMR spectrum of this compound could not be obtained due to

its poor solubility in common organic solvents.

Two other 2-(cinnamyloxy)benzaldehyde derivatives **68** and **69** were then

prepared by reacting substituted salicylaldehydes **66** and **67** (R = 3-OMe and 5-Br,

respectively) with cinnamyl bromide (**44**) under the alkylation conditions used previously

for similar substrates. The resulting aldehydes **68** and **69** were then employed in Povarov

reactions with 3-aminocoumarin (**25**) and *exo* adducts **70** and **71** were obtained in 89%

and 69% yield, respectively (Scheme 3.17). Enal **68**, was reacted with a variety of 3-

aminocoumarins (Table 3.2) to afford a series of pentacyclic heterocycles (**72-76**) in good

yields (75-86%). These reactions were usually complete within 1 hour. Thus, in a short

period of time, several pentacyclic heterocycles were prepared using solution phase

chemistry.

SCHEME 3.17 Synthesis of **70** and **71**

66, R = 3-OMe
67, R = 5-Br

68, R = 3-OMe
69, R = 5-Br

K$_2$CO$_3$, acetone,
reflux, 3-5 h

44

25

Yb(OTf)$_3$, CH$_3$CN
rt, 1-2 h, 69-89%

70, R = 3-OMe
71, R = 5-Br
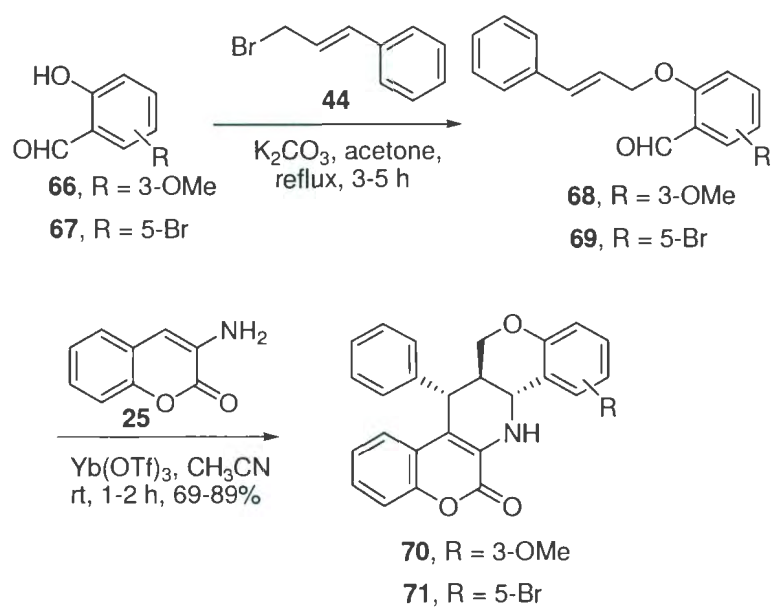
TABLE 3.2 Intramolecular Povarov Reactions between **59** and **68**
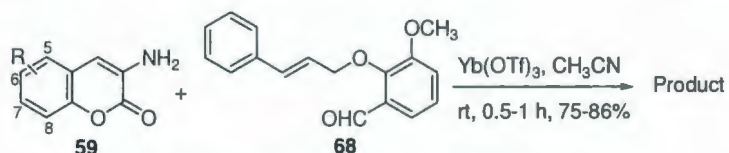
Entry	R	Product	Yield[a,b]
1	6-CH$_3$	**72**	84
2	6-OCH$_3$	**73**	85
3	6-Br	**74**	75
4	6-NO$_2$	**75**	78
5	8-OCH$_3$	**76**	86

[a] *endo/exo* ratio <5:95, determined by ^{1}H NMR analysis of the crude mixtures.

In all of the above examples, two new rings (both six-membered) were formed. Clearly, the length of the tether determines the size of the ring that is fused with the newly formed *N*-containing six-membered ring. An aldehyde having a shorter or longer tether (than the one studied so far), connecting the dienophile, was desired in order to test whether the length of the tether has a significant effect on the rate, yield and/or selectivity of the intramolecular Povarov reaction of coumarin-fused 2-azadienes. A pyrrole-based aldehyde **77**,[27] being available in the Bodwell laboratory, was selected as the nitrogen atom of the pyrrole system provides a handle for incorporating a cinnamyl tether. Careful investigation (Table 3.3) showed that selective *N*-alkylation of the aldehyde **77** could be performed by reacting it with cinnamyl bromide (**44**) in the presence of NaH in DMF at room temperature in 64% yield.

TABLE 3.3 Synthesis of **78**
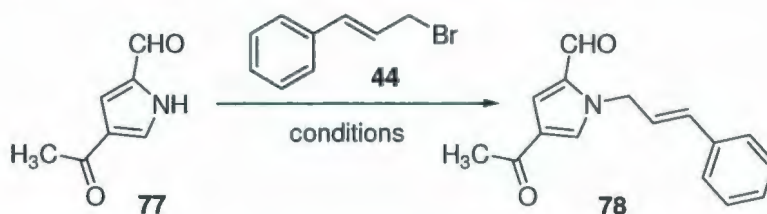
Entry	Reaction conditions	Yield (%)^a
1	KOH, CH$_2$Cl$_2$, reflux, 72 h	10
2	NaH, THF, reflux, 4 h	16
3	KOH, DMF, rt, 24 h	33
4	NaH, DMF, 0 °C, 2 h	64

^{a} Isolated yields

SCHEME 3.18 Povarov Reaction between **25** and **78**
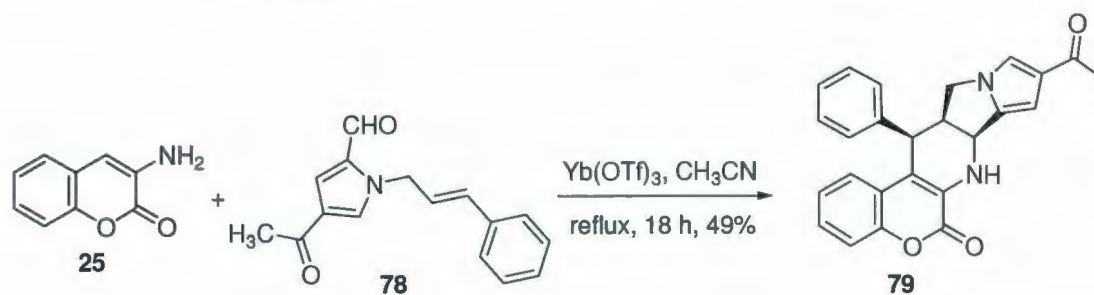
When subjected to the typical Povarov reaction conditions with 3-aminocoumarin (**25**), slow consumption of the starting materials was observed with the concomitant appearance of a major new compound. After stirring for 6 hours at room temperature, the reaction mixture was heated at reflux for 18 hours. Interestingly, compound **79**, which has *all-cis* stereochemistry, was formed in this reaction (Scheme 18). The all-*cis* relative stereochemistry was assigned based on standard 1D and 2D experiments (COSY, HMQC, HMBC). Thus, a [6,5,5] fused ring system could be prepared in a one-pot reaction from 3-aminocoumarin (**25**) and ketoaldehyde **78**. Clearly, the stereochemical outcome of this intramolecular Povarov reaction is different from those discussed previously. The fact that the *trans* relationship between the substituents on the dienophile is not maintained in the product points towards a stepwise mechanism. Presumably, the concerted pathway is disfavoured by the build-up of strain in the developing *trans*-[6,5] ring system.

3.3 Conclusion

In conclusion, a concise and highly diastereselective synthesis of functionalized pentacyclic heterocycles has been achieved using Povarov reactions involving an intramolecular IEDDA step. The insolubility of the *exo* (major) diastereomer in the reaction medium allows easy isolation and thus a very rapid access to a diverse set of pentacyclic heterocycles. For the most part, this study has utilized a four-atom tether and the major product is an isomer arising from an *exo* transition state for the intramolecular IEDDA reaction. The presence of a shorter tether (three atoms) results in a change in the stereochemical outcome of the reaction, which may be due to a change in mechanism.

3.4 Experimental

3.4.1 General Methods

All reactions were carried out without inert gas protection, unless otherwise mentioned. THF was dried and distilled over sodium/benzophenone. All other chemicals, including solvents, were used as received, without further purification. Thin layer chromatography (tlc) was performed on MN PolyGram precoated silica gel plates using 254 nm UV visualization. Flash chromatography was performed on silica gel columns. Melting points were recorded on Fisher-Johns apparatus and are uncorrected. All proton and carbon assignments are based on 2D experiments (COSY, HMQC, HMBC). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE spectrometer at 500.133 MHz and 125.770 MHz, respectively. Peaks reported are relative to internal standards: TMS ($\delta = 0.00$) for ^{1}H and CDCl$_3$ ($\delta = 77.23$), CD$_2$Cl$_2$ ($\delta = 54.00$) or DMSO-d_6 ($\delta = 39.51$) for ^{13}C spectra. Reported multiplicities are apparent. Infrared spectra were obtained on Bruker Tensor 27 instrument using neat samples. Low-resolution mass spectra were obtained using using Agilent 1100 series LC/MS chromatographic system and high-resolution mass spectra were obtained using Waters GCT Permier Micromass mass spectrometer.using neat samples. X-ray crystal structure was obtained on AFC8-Saturn single crystal X-ray diffractometer by David Miller, C-CART.

3.4.2 General Procedures

3.4.2.1 General Procedure 3-A

To a solution of 3-aminocoumarin in acetonitrile (~0.1 M solution) was added enal (1.05 equiv) and Yb(OTf)$_3$ (10 mol%) at room temperature. The resulting mixture was stirred at room temperature or heated at reflux as specified until complete consumption of the starting material (3-aminocoumarin) was observed by tlc analysis. The resulting slurry was subjected to suction filtration and the solids were washed with cold acetonitrile and air-dried to afford the product. The filtrate was subjected to flash chromatography depending upon the result of LC/MS analysis.

3.4.3 Synthesis and Characterization for Individual Compounds

3-(2-Allyloxybenzylamino)chromen-2-one (31), (7aS*, 13aR*)-5,6,7,7a,12,13,13a,14-Octahydro-5,12-Dioxa-7-azadibenzo[a,h]anthracen-6-one (32) and 5,6,12,13-Tetrahydro-5,12-dioxa-7-azadibenzo[a,h]anthracen-6-one (33)
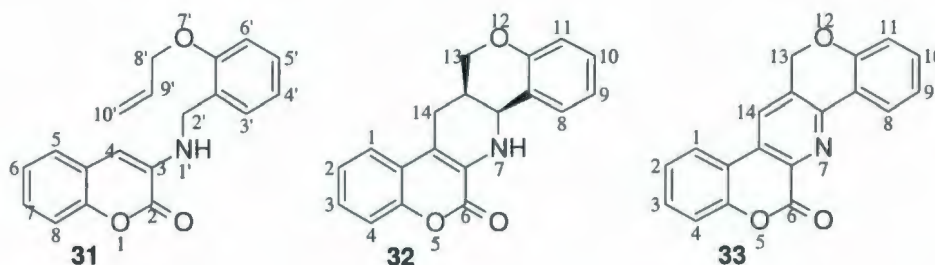
To a clear, colorless solution of enal **29** (0.087 g, 0.54 mmol) in acetonitrile (5.0 mL) was added 3-aminocoumarin (**25**) (0.082 g, 0.51 mmol) at room temperature followed by the addition of Yb(OTf)$_3$ (0.016 g, 0.026 mmol). The clear, colorless solution turned into a clear yellow solution instantaneously. The reaction mixture was stirred at room temperature for 3 h and then heated at reflux for 19 h. The solvent was removed under reduced pressure and the yellow residue was subjected to flash chromatography (0-10% ethyl acetate/petroleum ether) to afford **31** (0.061 g, 39%) as a pale yellow gum, **32** (0.026 g, 17%) as an off-white solid, **33** (0.029 g, 19%) as a white solid and recovered **25** (0.014 g, 17%) as an off-white solid.

31: δ_H(CDCl$_3$) = 7.29-7.24 (m, 4H), 7.22-7.15 (m, 2H), 6.95-6.90 (m, 2H), 6.38 (s, 1H, H-4), 6.13-6.06 (m, 1H, H-9′), 5.44 (dd, J = 16.8, 1.3 Hz, 1H, H-10′ *trans* to H-9′), 5.36

(br s, 1H, H-1′), 5.31 (dd, J = 10.8, 1.7 Hz, 1H, H-10′ cis to H-9′), 4.62 (dd, J = 3.6, 1.8 Hz, 2H, H-2′), 4.43 (d, J = 5.6 Hz, 2H, H-8′) ppm; δ_C(CDCl$_3$) = 159.9 (C-6), 156.5, 148.1, 133.3, 133.2, 128.94, 128.89, 125.8, 125.2, 124.7, 122.0, 121.0, 117.8, 116.2 (C-4), 111.9, 105.5, 69.0 (C-2′), 42.7 (C-8′) ppm; IR ν = 3412 (w), 1705 (s), 1627 (m), 1602 (w), 1574 (w), 1504 (m), 1456 (m), 1355 (w), 1287 (m), 1239 (m), 1167 (m), 1117 (w) cm^{-1}; MS m/z (relative intensity) = 308 (M$^+$+1, 21), 147 (M$^+$-160, 100); HRMS [M$^+$] calcd for C$_{19}$H$_{17}$NO$_3$ 307.1208 found 307.1211. **32**: mp = 212-214 °C (ethyl acetate/hexanes); δ_H(CDCl$_3$) = 7.38-7.37 (m, 1H), 7.29-7.25 (m, 3H), 7.24-7.21 (m, 2H), 6.93 (t, J = 7.0 Hz, 1H), 8.87 (d, J = 8.0 Hz, 1H), 5.07 (s, 1H, H-7), 4.53 (s, 1H, H-7a), 4.22-4.14 (m, 2H, H-13), 3.03 (dd, J = 18.3, 6.8 Hz, 1H, H-14β), 2.72 (dd, J = 18.5, 4.5 Hz, 1H, H-14α), 2.68-2.64 (m, 1H, H-13a) ppm; δ_C(CDCl$_3$) = 158.3 (C-6), 153.9, 148.1, 129.9, 129.1, 126.5, 126.2, 124.8, 122.6, 121.5, 121.3, 121.1, 117.1, 116.7, 114.6, 66.7 (C-13), 47.5 (C-7a), 28.7 (C-14), 22.8 (C-13a) ppm; IR ν = 3331 (m), 1701 (s), 1612 (w), 1578 (m), 1501 (w), 1484 (m), 1469 (w), 1431 (m), 1339 (w), 1322 (w), 1289 (m), 1255 (m), 1232 (m), 1195 (s), 1127 (w), 1074 (w), 1029 (m), 1009 (w) cm^{-1}; MS m/z (relative intensity) = 307 (M$^+$+2, 21), 306 (M$^+$+1, 100), 304 (14), 302 (72), 174 (17); HRMS [M$^+$] calcd for C$_{19}$H$_{15}$NO$_3$ 305.1052 found 305.1048. **33**: mp = 222-224 °C; δ_H(DMSO) = 8.79 (s, 1H), 8.30 (m, 1H), 8.24 (dd, J = 7.6, 1.0 Hz, 1H), 7.64-7.61 (m, 1H), 7.48-7.46 (m, 3H), 7.21 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 5.50 (s, 2H) ppm; δ_C(DMSO) = 157.9 (C-6), 156.6, 150.5, 149.1, 137.3, 132.6, 132.1, 131.2, 130.8, 127.6, 124.8, 123.8, 122.6, 121.6, 117.3, 117.1, 116.9, 67.2 (C-13) ppm; IR ν = 1742 (s), 1608 (m), 1509 (s),

1432 (m), 1339 (s), 1177 (w), 1026 (s) cm^{-1}; MS m/z (relative intensity) = 303 (M$^+$+2, 23), 302 (M$^+$+1, 100); HRMS [M$^+$] calcd for $C_{19}H_{11}NO_3$ 301.0739 found 301.0741.

5,6,12,13-Tetrahydro-5,12-dioxa-7-azadibenzo[*a,h*]anthracen-6-one (33)
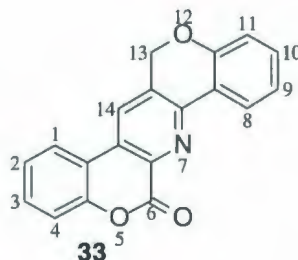
To a clear, colorless solution of 3-aminocoumarin (**25**) (0.161 g, 1.00 mmol) in acetonitrile (10.0 mL) was added aldehyde **34** (0.168 g, 1.05 mmol) followed by Yb(OTf)$_3$ (0.031 g, 5 mol%). The reaction mixture was heated at reflux for 9 d, during which time the reaction mixture became a yellow suspension. After cooling to room temperature, the reaction mixture was subjected to suction filtration and the solids were washed with cold dichloromethane and air-dried to afford **33** as a yellow solid (0.111 g, 37%). The filtrate was concentrated and purified by flash chromatography on silica gel (20% ethyl acetate/ light petroleum ether) to afford a second batch of **33** (0.029 g, 10%) as an off-white solid and recovered 3-aminocoumarin (**25**) (0.030 g, 19%) as an off-white solid. Combined yield of **33** = 0.140 g (47%).

14-Phenyl-5,6,12,13-tetrahydro-5,12-dioxa-7-azadibenzo[*a,h*]anthracen-6-one (43)
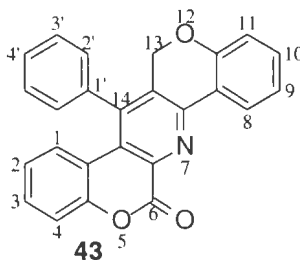
To a clear, colorless solution of 3-aminocoumarin (**25**) (0.081 g, 0.50 mmol) in acetonitrile (5.0 mL) was added ynal **42** (0.125 g, 0.525 mmol) and Yb(OTf)$_3$ (0.031 g, 10 mol%). The resulting yellow suspension was stirred at room temperature for 3 h. The reaction mixture was then heated at reflux for 72 h. The mixture was cooled to room temperature. The precipitate was isolated by suction filtration, washed with acetonitrile and air-dried to afford **43** as a white solid (0.085 g, 45%). mp = 277-279 °C (decomp); δ_H(CD$_2$Cl$_2$) = 8.35 (d, J = 7.8 Hz, 1H), 7.55-7.54 (m, 3H), 7.32 (t, J = 7.5 Hz, 1H), 7.28-7.27 (m, 2H), 7.23-7.22 (m, 2H), 7.10 (t, J = 7.2 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 6.77-6.72 (m, 2H), 4.94 (s, 2H) ppm; δ_C(CD$_2$Cl$_2$) = 159.3 (C-6), 157.2, 151.6, 150.2, 144.6, 139.2, 136.8, 133.2, 131.6, 130.9, 130.8, 130.0, 129.5, 128.5, 127.9, 126.3, 124.3, 123.3, 122.6, 118.3, 118.1, 117.5, 66.7 (C-13) ppm; MS *m/z* (relative intensity) = 379 (M$^+$+2, 29), 378 (M$^+$+1, 100); HRMS [M$^+$] calcd for C$_{25}$H$_{15}$NO$_3$ 377.1052 found 377.1049.

2-(Cinnamyloxy)benzaldehyde (45)
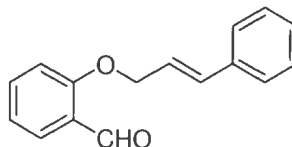
A mixture of salicylaldehyde (**41**) (0.54 g, 4.4 mmol), anhydrous K_2CO_3 (0.61 g, 4.4 mmol), cinnamyl bromide (**44**) (0.79 g, 4.0 mmol) and acetone (20 mL) was stirred at room temperature under a nitrogen atmosphere for 16 h. The mixture was subjected to suction filtration and the solids were washed with acetone. The filtrate was concentrated under reduced pressure and the residue was redissolved in chloroform. The resulting solution was washed sequentially with 1 M NaOH solution and brine. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was crystallized from ethyl acetate/hexanes to afford **45** (0.88 g, 91% yield). mp = 51-52 °C (lit.[20] 50-51 °C). δ_H(CDCl$_3$) = 10.57 (s, 1H, *CHO*), 7.85 (dd, J = 7.7, 1.8 Hz, 1H), 7.55-7.51 (m, 1H), 7.41 (d, J = 7.7 Hz, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.28-7.24 (m, 1H), 7.05-7.02 (m, 2H), 6.76 (d, J = 15.3 Hz, 1H), 6.42 (dt, J = 15.4, 5.6 Hz, 1H), 4.81 (dd, J = 5.7, 1.5 Hz, 2H) ppm; δ_C(CDCl$_3$) = 189.9, 161.2, 136.3, 136.0, 133.7, 128.9, 128.7, 128.4, 126.8, 125.4, 123.6, 121.1, 113.1, 69.4 ppm.

**(7a*R**, 13a*R**, 14*S**)-14-Phenyl-5,6,7,7a,12,13,13a,14-octahydro-5,12-dioxa-7-azadibenzo[*a,h*]anthracen-6-one (46)**
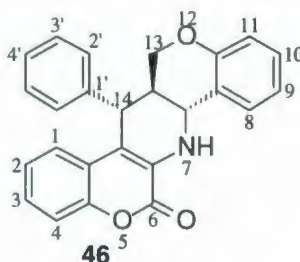
Method 1: To a clear, colorless solution of 3-aminocoumarin (**25**) (0.040 g, 0.25 mmol) in acetonitrile (2.5 mL) was added enal **45** (0.062 g, 0.26 mmol) followed by Yb(OTf)$_3$ (0.008 g, 5 mol%). The resulting clear, yellow solution was stirred at room temperature for 1 h. The reaction turned into a pale yellow suspension over the course of the reaction. The product was isolated by suction filtration and washed with cold acetonitrile to afford **46** as an off-white solid (0.053 g, 56%).

Method 2: According to general procedure 3-A, 3-aminocoumarin (**25**) (0.097 g, 0.60 mmol), enal **45** (0.15 g, 0.63 mmol) and Yb(OTf)$_3$ (0.037 g, 10 mol%) afforded **46** as a white solid (0.195 g, 85%). mp = 268-269 °C; δ_H(CD$_2$Cl$_2$) = 7.36 (d, J = 7.7 Hz, 1H), 7.30-7.28 (m, 2H), 7.27-7.26 (m, 2H), 7.25-7.23 (m, 3H), 7.21-7.19 (m, 1H), 7.07-7.05 (m, 1H), 6.98-6.95 (m, 2H), 6.85 (d, J = 7.4 Hz, 1H), 5.49 (s, 1H, H-7), 4.42 (d, J = 11.1 Hz, 1H, H-7a), 4.36 (dd, J = 10.6, 3.1 Hz, 1H, H-13α), 4.11 (t, J = 10.6 Hz, 1H, H-β), 3.98 (d, J = 11.0 Hz, 1H, H-14), 2.44-2.39 (m, 1H, H-13a) ppm; δ_C(CD$_2$Cl$_2$) = 159.1 (C-6), 154.4, 150.5, 149.0, 142.5, 132.1, 129.5, 129.4, 129.1, 126.7, 125.7, 125.5, 124.7, 124.2, 121.5, 121.2, 120.8, 117.3, 116.7, 66.9 (C-12), 52.0 (C-7), 45.0 (C-13a), 44.0 (C-

14) ppm; IR ν = 3334 (m), 1702 (s), 1618 (w), 1581 (w), 1492 (m), 1475 (w), 1445 (w), 1347 (m), 1322 (m), 1287 (w), 1252 (m), 1229 (m), 1191 (s), 1129 (w), 1116 (w), 1074 (w), 1050 (m), 1028 (w), 1012 (w) cm^{-1}; MS m/z (relative intensity) = 383 (M$^+$+2, 14), 382 (M$^+$+1, 53), 380 (29), 379 (29), 378 (100); HRMS [M$^+$] calcd for C$_{25}$H$_{19}$NO$_3$ 381.1365, found 381.1371.

(E)-Cinnamic acid 2-formylphenyl ester (48)
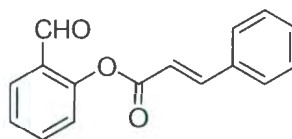
A mixture of salicylaldehyde (41) (0.244 g, 2.00 mmol), $trans$-cinnamic acid (47) (0.445 g, 3.00 mmol), DCC (0.619 g, 3.00 mmol) and DMAP (0.037 g, 0.30 mmol) in dichloromethane (5.00 mL) was stirred at room temperature for 3 h. The mixture was then diluted with dichloromethane (20 mL) and successively washed with water (2 × 10 mL), NaHSO$_4$ solution (10 mL), saturated NaHCO$_3$ solution (10 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (10-15% ethyl acetate/hexanes) to afford 48 as a white solid (0.455 g, 90%). mp = 76-77 °C (lit.[21] 76.1-76.5 °C). δ_H(CDCl$_3$) = 10.21 (s, 1H, CHO), 7.96-7.93 (m, 2H), 7.66-7.64 (m, 1H), 7.62 (br m, 2H), 7.44-7.40 (m, 4H), 7.29 (d, J = 7.9 Hz, 1H), 6.70 (d, J = 15.9

Hz, 1H) ppm; δ_C(CDCl$_3$) = 188.8 (*CHO*), 165.3, 152.3, 147.8, 135.4, 133.9, 131.2. 130.1.

129.2. 128.5, 128.2, 126.3, 123.5, 116.3 ppm

(*E*)-2,3-Dimethoxycinnamic acid 2-formylphenyl ester (51)

51
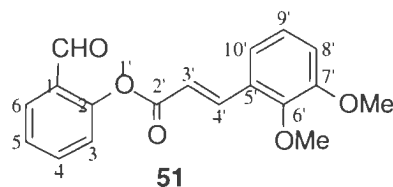
A mixture of salicylaldehyde (**41**) (0.244 g, 2.00 mmol), 2,3-dimethoxy *trans*-cinnamic acid (**50**) (0.625 g, 3.00 mmol), DCC (0.619 g, 3.00 mmol) and DMAP (0.049 g, 0.40 mmol) in dichloromethane (10 mL) was stirred at room temperature for 24 h and then heated at reflux for 24 h. The mixture was cooled to room temperature, diluted with dichloromethane (20 mL) and successively washed with water (2 × 10 mL), NaHSO$_4$ (10 mL), saturated NaHCO$_3$ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography on silica gel column (10-15% ethyl acetate/hexanes) to afford **51** as a colorless oil (0.112 g, 18%). δ_H(CDCl$_3$) = 10.23 (s, 1H, *CHO*), 8.25 (d, *J* = 16.7 Hz, 1H, H-3), 7.94 (dd, *J* = 7.5, 1.4 Hz, 1H, H-3′), 7.68-7.64 (m, 1H, H-5′), 7.40 (t, *J* = 7.6 Hz, 1H, H-4′), 7.29 (d, *J* = 8.1 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H, H-6′), 7.12 (t, *J* = 8.4 Hz, 1H, H-8), 7.00 (d, *J* = 8.5 Hz, 1H), 6.75 (d, 16.7 Hz, 1H, H-2), 3.91 (s, 3H), 3.90 (s, 3H) ppm; δ_C(CDCl$_3$) = 188.7 (*CHO*), 165.5, 153.4, 152.6,

149.1, 142.8, 135.5, 130.0, 128.2, 126.5, 124.5, 123.7, 119.8, 117.6, 114.9, 61.6, 56.1 ppm; IR ν = 2765 (w), 1743 (m), 1701 (s), 1636 (s), 1602 (s), 1576 (m), 1480 (w), 1448 (m), 1404 (w), 1309 (m), 1262 (w), 1195 (m), 1156 (m), 1123 (s) cm^{-1}; MS m/z (relative intensity) = M^{+} was not found, 287 (100).

2-(4-Bromocinnamyloxy)benzaldehyde (55)

55
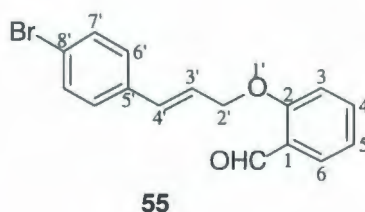
A mixture of salicylaldehyde (**41**) (0.147 g, 1.20 mmol), bromide **53** (0.348 g, 1.26 mmol) and anhydrous K_2CO_3 (0.174 g, 1.26 mmol) in acetone (12.0 mL) was heated at reflux for 4.5 h. The reaction mixture was then allowed to cool to room temperature and filtered through a pad of Celite® under suction and washed with acetone. The solvent was removed from the filtrate under reduced pressure and the residue was subjected to flash chromatography (5-10% ethyl acetate/hexanes) to afford **55** as a white solid (0.308 g, 81%). mp = 83-84 °C. δ_H(CDCl$_3$) = 10.56 (s, 1H, *CHO*), 7.86 (dd, J = 7.7, 2.3 Hz, 1H), 7.56-7.53 (m, 1H), 7.47 (m, 2H), 7.28 (m, 2H), 7.07-7.02 (m, 2H), 6.71 (d, J = 15.4 Hz, 1H, H-4'), 6.42 (dt, J = 15.6, 5.9 Hz 1H, H-3'), 4.82 (d, J = 5.3 Hz, 2H, H-2') ppm; δ_C(CDCl$_3$) = 189.9 (*CHO*), 161.1, 136.1, 135.3, 132.4, 132.0, 128.9, 128.3, 125.4, 124.5, 122.2, 121.3 (C-3'), 113.1 (C-2'), 69.1 (C-1') ppm; MS m/z (relative intensity) = 318

(M$^+$+2, 15), 317 (M$^+$+1, 15), 315 (18), 299 (54), 197 (74), 116 (100), 99 (16); HRMS [M$^+$] calcd for C$_{16}$H$_{13}$BrO$_2$ 316.0099, found 316.0097.

2-(4-Nitrocinnamyloxy)benzaldehyde (56)

56
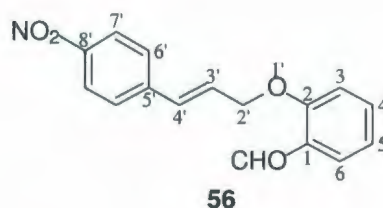
A mixture of salicylaldehyde (**41**) (0.140 mL, 1.33 mmol), bromide **54** (0.339 g, 1.40 mmol) and anhydrous K$_2$CO$_3$ (0.194 g, 1.40 mmol) in acetone (10.0 mL) was heated at reflux for 4 h. The reaction mixture was then allowed to cool to room temperature and suction filtered through a pad of Celite®. The filter cake was washed with acetone and the solvent was removed from the filtrate under reduced pressure. The yellow residue was subjected to flash chromatography (5-20% ethyl acetate/petroleum ether) to afford **56** as a pale yellow solid (0.254 g, 67%) and recovered starting material **41** (0.049 g, 30%) as a colorless liquid. **56:** mp = 91-92 °C. δ_H(CDCl$_3$) = 10.57 (s, 1H, *CHO*), 8.20 (m, 2H, H-7′), 7.87 (dd, *J* = 7.5, 1.1 Hz, 1H, H-6), 7.58-7.55 (m, 3H, H-4, H-6′), 7.08 (t, *J* = 7.2 Hz, 1H, H-5), 7.04 (d, *J* = 7.9 Hz, 1H, H-3), 6.86 (d, *J* = 15.8 Hz, 1H, H-4′), 6.62 (dt, *J* = 15.3, 4.9 Hz, 1H, H-3′), 4.89 (dd, *J* = 5.2, 2.2 Hz, 2H, H-2′) ppm; δ_C(CDCl$_3$) = 189.7 (*CHO*), 160.8 (C-2), 147.5 (C-8′), 142.7 (C-5′), 136.1 (C-4), 130.8 (C-4′), 129.0

(C-6), 128.6 (C-3′), 127.3 (C-6′), 125.4 (C-1), 124.3 (C-7′), 121.5 (C-5), 113.0 (C-3), 68.6 (C-2′) ppm; MS m/z (relative intensity) = M$^+$ not observed, 266 (M$^+$–17, 22), 214 (100). HRMS [M$^+$] calcd for $C_{16}H_{13}NO_4$ 283.0845 found 283.0844.

(7aR*, 13aR*, 14S*)-14-(4-Bromophenyl)- 5,6,7,7a,12,13,13a,14-octahydro-5,12-dioxa-7-azadibenzo[a,h]anthracen-6-one (57)
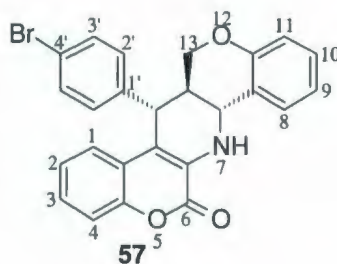
According to general procedure 3-A, 3-aminocoumarin (**25**) (0.135 g, 0.840 mmol), enal **55** (0.28, 0.88 mmol) and Yb(OTf)$_3$ (0.052 g, 10 mol%) afforded **57** as a white solid (0.32 g, 84%). mp = 276-278 °C; δ_H(CD$_2$Cl$_2$) = 7.48 (d, J = 7.1 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.26-7.22 (m, 2H), 7.16-7.15 (m, 2H), 7.07 (t, J = 6.9 Hz, 1H), 7.01-6.98 (m, 2H), 6.87 (d, J = 7.1 Hz, 1H), 5.51 (s, 1H, H-7), 4.43 (d, J = 10.8 Hz, 1H, H-7a), 4.34 (dd, J = 10.4 Hz, 2.7 Hz, 1H, H-13α), 4.10 (t, J = 10.4 Hz, 1H, H-13β), 3.97 (d, J = 10.9 Hz, 1H, H-14), 2.41-2.34 (m, 1H) ppm; due to very low solubility of this compound, a satisfactory ^{13}C NMR spectrum could not be obtained; the following major signals were observed: δ_C(CD$_2$Cl$_2$) = 141.7, 132.6, 132.0, 129.5, 126.8, 125.4, 124.5, 124.4, 121.3, 117.3, 116.8, 66.7 (C-13), 51.9 (C-7a), 44.9 (C-13a), 43.4 (C-14) ppm; IR v = 3389 (w), 1704 (s), 1628 (m), 1555 (w), 1462 (m), 1457 (w), 1428 (w),

1346 (m), 1322 (w), 1281 (w), 1260 (w), 1238 (m), 1189 (m), 1172 (m), 1051 (m) cm^{-1}; HRMS [M$^+$] calcd for $C_{25}H_{18}NO_3Br$ 459.0470, found 459.0471.

(7aR*, 13aR*, 14S*)-14-(4-Nitrophenyl)- 5,6,7,7a,12,13,13a,14-octahydro-5,12-- dioxa-7-azadibenzo[a,h]anthracen-6-one (58)
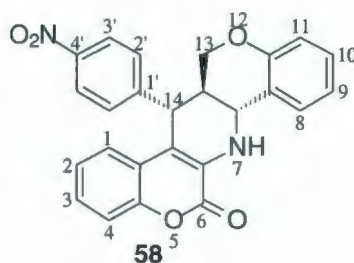
According to general procedure 3-A, 3-aminocoumarin (**25**) (0.055 g, 0.34 mmol), enal **56** (0.10, 0.36 mmol) and Yb(OTf)$_3$ (0.021 g, 10 mol%) afforded **58** as a pale yellow solid (0.104, 72%). mp = 239-240 °C; δ_H(CD$_2$Cl$_2$) = 8.17 (m, 2H), 7.43-7.41 (m, 3H), 7.34 (d, J = 7.4 Hz, 1H), 7.25-7.18 (m, 2H), 7.04 (t, J = 7.5 Hz, 1H), 6.94 (t, J = 7.2 Hz, 1H), 6.84 (d, J = 7.7 Hz, 2H), 5.55 (s, 1H, H-7), 4.45 (d, J = 10.7 Hz, 1H, H-7a), 4.29 (dd, J = 10.3, 3.2 Hz, 1H, H-13α), 4.13-4.09 (m, 2H), 2.39-2.35 (m, 1H, H-13a) ppm; δ_C(CD$_2$Cl$_2$) = 159.0 (C-6), 154.4, 150.5, 149.2, 147.9, 132.7, 129.9, 129.6, 127.2, 125.7, 125.0, 124.7, 124.3, 121.7, 121.2, 120.4, 119.5, 117.6, 117.2, 66.7 (C-12), 52.1 (C-7a), 44.9 (C-13a), 44.0 (C-14) ppm; IR v = 3401 (w), 1705 (s), 1629 (m), 1552 (m), 1489 (m), 1448 (w), 1431 (m), 1327 (w), 1277 (w), 1258 (w), 1236 (m), 1181 (m), 1176 (w), 1042 (m) cm^{-1}; MS m/z (relative intensity) = 413 (M$^+$+2, 30), 412 (M$^+$+1, 100). HRMS [M$^+$] calcd for $C_{25}H_{18}N_2O_5$ 426.1216, found 426.1211.
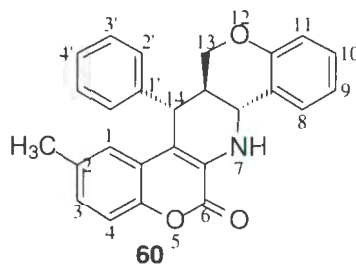
(7a*R**, 13a*R**, 14*S**)-2-Methyl-14-phenyl-5,6,7,7a,12,13,13a,14-octahydro-5,12-dioxa-7-azadibenzo[*a,h*]anthracen-6-one (60)

According to general procedure 3-A, 3-amino-6-methylcoumarin (0.105 g, 0.600 mmol), enal **45** (0.15, 0.63 mmol) and Yb(OTf)$_3$ (0.037 g, 10 mol%) afforded **60** as an off-white solid (0.206, 87%). mp = 228-229 °C; δ_H(CD$_2$Cl$_2$) = 7.24-7.21 (m, 2H), 7.19-7.17 (m, 2H), 7.15-7.11 (m, 3H), 7.10-7.07 (m, 1H), 6.94-6.91 (m, 1H), 8.86-6.83 (m, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 5.43 (s, 1H, H-7), 4.34 (d, *J* = 10.8 Hz, 1H, H-7a), 4.29 (dd, *J* = 10.7, 3.5 Hz, 1H, H-13α), 3.96 (t, *J* = 11.0 Hz, 1H, H-13β), 3.88 (d, *J* = 11.1 Hz, 1H, H-14), 2.32-2.24 (m, 1H, H-13a), 2.23 (s, 3H, C-2-*CH₃*) ppm; δ_C(CD$_2$Cl$_2$) = 159.4 (C-6), 152.3, 149.3, 142.7, 132.4, 130.9, 130.3, 129.6, 128.7, 127.8, 126.8, 125.9, 124.9, 124.4, 121.4, 121.2, 121.0, 117.2, 116.9, 67.1 (C-13), 52.2 (C-7a), 45.3 (C-13a), 44.3 (C-14), 20.8 (C-2-*CH₃*) ppm; IR *v* = 3366 (w), 1727 (s), 1699 (w), 1684 (w), 1652 (w), 1628 (m), 1558 (m), 1541 (w), 1499 (s), 1465 (m), 1340 (m), 1323 (m), 1287 (w), 1257 (m), 1222 (m), 1192 (m), 1180 (m), 1117 (m), 1073 (w), 1048 (m), 1036 (m) cm^{-1}; MS *m/z* (relative intensity) = 397 (M$^+$+2, 28), 396 (M$^+$+1, 100), 395 (16), 394 (22), 392 (47). HRMS [M$^+$] calcd for C$_{26}$H$_{21}$NO$_3$ 395.1521 found 395.1520.
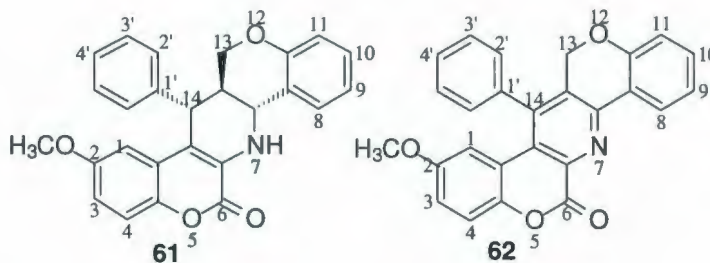
(7a*R**, 13a*R**, 14*S**)-2-Methoxy-14-phenyl-5,6,7,7a,12,13,13a,14-octahydro-5,12-dioxa-7-azadibenzo[*a,h*]anthracen-6-one (61) and 2-Methoxy-14-phenyl-5,6,12,13-tetrahydro-5,12-dioxa-7-azadibenzo[*a,h*]anthracen-6-one (62)

According to general procedure, 3-amino-6-methoxycoumarin (0.076 g, 0.40 mmol), enal **45** (0.10 g, 0.42 mmol) and Yb(OTf)$_3$ (0.025 g, 10 mol%) afforded **61** as an off-white solid (0.14 g, 84%). Additionally, flash chromatography (ethyl acetate) of the filtrate afforded **62** as a white solid (0.003 g, 2%). **61**: mp = 228-229 °C. δ_H(CD$_2$Cl$_2$) = 7.41 (d, *J* = 7.1 Hz, 1H, H-8), 7.35-7.32 (m, 2H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.26-7.20 (m, 3H), 7.17 (d, *J* = 8.8 Hz, 1H, H-4), 7.02 (t, *J* = 7.4 Hz, 1H, H-9), 6.82 (d, *J* = 8.4 Hz, 1H, H-11), 6.73 (dd, *J* = 8.9, 2.1 Hz, 1H, H-3), 6.42 (d, *J* = 2.0 Hz, 1H, H-1), 5.49 (s, 1H, H-7), 4.41 (d, *J* = 10.2 Hz, 1H, H-7a), 4.32 (dd, *J* = 10.7, 3.0 Hz, 1H, H-13α), 4.07 (t, *J* = 11.1 Hz, 1H, H-13β), 3.91 (d, *J* = 11.3 Hz, 1H, H-14), 3.42 (s, 3H, C-2-O*CH$_3$*), 2.41 (m, 1H, H-13a) ppm; δ_C(CD$_2$Cl$_2$) = 159.3 (C-6), 156.2, 154.6, 143.5, 142.7, 132.5, 129.7, 129.6, 128.7, 127.9, 125.6 (C-8), 121.6, 121.5 (C-9), 121.4, 120.9, 117.7, 117.5 (C-11), 114.4 (C-3), 107.9 (C-1), 67.2 (C-13), 55.9 (C-2-O*CH$_3$*), 52.1 (C-7a), 44.8 (C-14), 44.4 (C-13a) ppm; IR v = 3360 (w), 1702 (s), 1614 (w), 1560 (w), 1499 (m), 1467 (w), 1451

(w), 1426 (w), 1343 (m), 1319 (w), 1282 (w), 1258 (w), 1234 (w), 1187 (m), 1170 (m), 1050 (m) cm^{-1}; MS m/z (relative intensity) = 413 (M$^+$+2, 30), 412 (M$^+$+1, 100), 411 (39), 410 (69), 408 (65). HRMS [M$^+$] calcd for $C_{26}H_{21}NO_4$ 411.1471, found 411.1465. **62**: mp = 273-274 °C (decomp); δ_H(CDCl$_3$) = 8.54 (dd, J = 7.6, 2.4 Hz, 1H), 7.68-7.65 (m, 2H), 7.59 (d, J = 7.3 Hz, 1H), 7.40-7.38 (m, 1H), 7.35 (d, J = 6.5 Hz, 1H), 7.27-7.26 (m, 1H), 7.18 (t, J = 7.6 Hz, 1H), 6.94-6.90 (m, 2H), 6.47 (d, J = 7.0 Hz, 1H), 4.98 (s, 2H), 3.29 (s, 3H) ppm; δ_C(CDCl$_3$) = due to small quantity and low solubility of this compound, ^{13}C NMR could not be obtained. IR ν = 1734 (s), 1597 (w), 1561 (w), 1499 (m), 1465 (s), 1431 (m), 1376 (m), 1294 (m), 1252 (m), 1215 (s), 1190 (m), 1153 (s), 1110 (m), 1085 (w), 1061 (w), 1039 (s), 1020 (m) cm^{-1}; MS m/z (relative intensity) = 409 (M$^+$+2, 26), 408 (M$^+$+1, 100); HRMS [M$^+$] calcd for $C_{26}H_{17}NO_4$ 407.1158, found 407.1160

(7aR*, 13aR*, 14S*)-2-Bromo-14-phenyl-5,6,7,7a,12,13,13a,14-octahydro-5,12-dioxa-7-azadibenzo[a,h]anthracen-6-one (63)

63
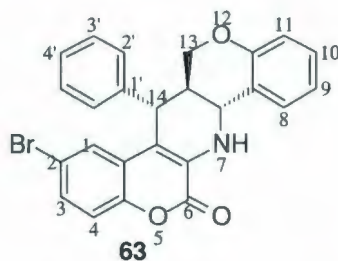
According to general procedure 3-A, 3-amino-6-bromocoumarin (0.072 g, 0.30 mmol), enal **45** (0.075, 0.32 mmol) and Yb(OTf)$_3$ (0.019 g, 10 mol%) afforded **63** as a

white solid (0.11, 78%). mp = 273-274 °C; δ_H(DMSO-d_6) = 7.68 (dd, J = 7.2, 2.6 Hz, 1H, H-3), 7.40-7.37 (m, 3H), 7.34-7.30 (m, 4H), 7.24 (m, 1H), 7.22-7.21 (m, 1H), 7.19 (dd, J = 7.8, 2.8 Hz, 1H), 6.68 (d, J = 8.4 Hz, 1H, H-11), 6.08 (s, 1H, H-7), 4.42 (d, J = 10.2 Hz, 1H, H-7a), 4.29-4.04 (m, 3H), 2.13-2.05 (m, 1H, H-13a) ppm; δ_C(CD$_2$Cl$_2$) = 159.1 (C-6), 154.5, 150.4, 149.2, 147.9, 131.6, 130.0, 129.7, 127.2, 125.6, 125.0, 124.8, 124.4, 121.6, 121.3 (C-9), 120.4, 119.6, 117.5, 117.2 (C-11), 66.7 (13), 52.1 (C-7a), 44.9 (C-14), 44.0 (C-13a) ppm; IR ν = 3392 (w), 1703 (s), 1620 (m), 1595 (w), 1583 (w), 1559 (w), 1488 (s), 1458 (m), 1410 (m), 1343 (s), 1310 (m), 1275 (m), 1254 (w), 1230 (w), 1217 (m), 1201 (s), 1137 (w), 1077 (m), 1048 (s), 1024 (m), 1009 (m) cm^{-1}; HRMS [M$^+$] calcd for C$_{25}$H$_{18}$NO$_3$Br 459.0470, found 459.0468.

(7aR*, 13aR*, 14S*)-2-Nitro-14-phenyl-5,6,7,7a,12,13,13a,14-octahydro-5,12-dioxa-7-azadibenzo[a,h]anthracen-6-one (64)
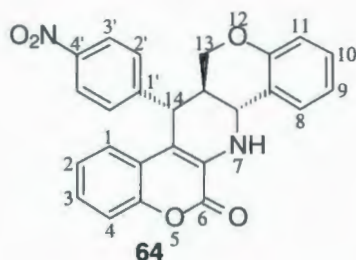
According to general procedure 3-A, 3-amino-6-nitrocoumarin (0.062 g, 0.30 mmol), enal **45** (0.075 g, 0.32 mmol) and Yb(OTf)$_3$ (0.019 g, 10 mol%) afforded **64** as a pale yellow solid (0.105 g, 82%). mp = 262-263 °C; δ_H(CD$_2$Cl$_2$) = 8.00 (dd, J = 9.0 Hz,

1.8 Hz, 1H, H-3), 7.82 (d, J = 2.4 Hz, 1H, H-1), 7.41-7.36 (m, 4H), 7.33-7.18 (m, 4H),

7.04 (t, J = 7.8 Hz, 1H, H-10), 6.82 (t, J = 7.3 Hz, 1H, H-9), 5.61 (s, 1H, H-7), 4.49 (d, J

= 10.4 Hz, 1H, H-7a), 4.29 (dd, J = 10.3, 3.2 Hz, 1H, H-13α), 4.04 (t, J = 10.3 Hz, 1H,

H-13β), 3.99 (d, J = 10.6 Hz, 1H, H-14), 2.48-2.40 (m, 1H, H-13a) ppm; $\delta_C(CD_2Cl_2)$ =

158.7 (C-6), 152.3 151.2, 144.0, 140.9, 132.4, 130.0, 129.8, 128.4, 128.3, 128.0, 125.4,

121.6, 121.5, 120.5, 120.4, 119.4, 119.2, 117.5, 67.8 (C-13), 52.2 (C-7a), 42.1 (C-13a),

41.9 (C-14) ppm; IR ν = 3354 (m), 1718 (s), 1583 (w), 1527 (s), 1490 (s), 1336 (s), 1254

(m), 1234 (w), 1185 (m), 1105 (w), 1049 (m) cm^{-1}; MS m/z (relative intensity) = (M$^+$+2,

27), (M$^+$+1, 100); HRMS [M$^+$] calcd for $C_{25}H_{18}N_2O_5$ 426.1216, found 426.1215.


(7aR*, 13aR*, 14S*)-4-Methoxy-14-phenyl-5,6,7,7a,12,13,13a,14-octahydro-5,12-dioxa-7-azadibenzo[a,h]anthracen-6-one (65)
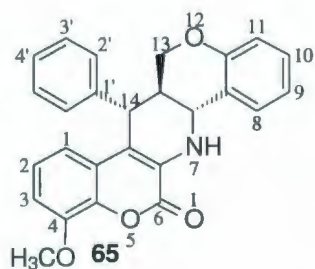

According to general procedure 3-A, 3-amino-8-methoxycoumarin (0.076 g, 0.40

mmol), enal **45** (0.10, 0.42 mmol) and Yb(OTf)$_3$ (0.025 g, 10 mol%) afforded **65** as an

off-white solid (0.141, 86%). mp = 276-278 °C; $\delta_H(CD_2Cl_2)$ = 7.33 (d, J = 7.6 Hz, 1H), 7.

23 (m, 2H), 7.16 (m, 1H), 7.12 (m, 3H), 6.93 (t, J = 7.3 Hz, 1H), 6.78 (t, J = 7.8 Hz, 1H),

6.74 (d, J = 7.8 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.51 (d, J = 8.3 Hz, 1H), 5.37 (s, 1H, H-7), 4.30 (d, J = 10.3 Hz, 1H, H-7a), 4.24 (dd, J = 10.7, 3.3 Hz, 1H, H-13α), 3.98 (t, J = 11.0 Hz, 1H, H-13β), 3.84 (d, J = 10.5 Hz, 1H, H-14), 3.83 (s, 3H, C-4-OCH_3), 2.29 (m, 1H, H-13a) ppm; δ_C(CD_2Cl_2) = 158.9 (C-6), 154.6, 147.8, 142.9, 138.8, 132.5, 129.6, 128.7, 127.8, 125.7, 124.1, 121.8, 121.7, 121.6, 121.4, 117.5, 116.7, 109.4, 67.1 (C-13), 56.7 (C-4-OCH_3), 52.2 (C-7a), 45.2 (C-13a), 44.4 (C-14) ppm (one carbon signal fewer than expected) ppm; IR v = 3332 (m), 1682 (s), 1622 (w), 1600 (w), 1575 (m), 1483 (m), 1452 (m), 1345 (m), 1281 (m), 1260 (w), 1223 (m), 1212 (m), 1197 (m), 1179 (s), 1133 (w), 1108 (w), 1063 (w), 1050 (w), 1028 (m), 1003 (m) cm^{-1}; MS m/z (relative intensity) = 413 (M$^+$+2, 27), 412 (M$^+$+1, 100), 411 (25), 410 (48), 408 (43); HRMS [M$^+$] calcd for $C_{26}H_{21}NO_4$ 411.1471, found 411.1474.

2-(Cinnamyloxy)-3-methoxybenzaldehyde (68)

68
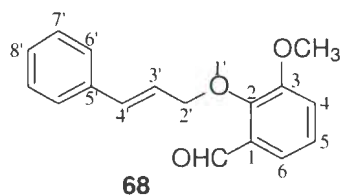
A mixture of *o*-vanillin (0.46 g, 3.0 mmol), cinnamyl bromide (0.62 g, 3.2 mmol) (**44**) and anhydrous K_2CO_3 (0.44 g, 3.2 mmol) in acetone (30 mL) was heated at reflux for 3 h. The reaction mixture was allowed to cool to room temperature and then suction filtered through a pad of Celite® and the filter cake was washed with acetone. The
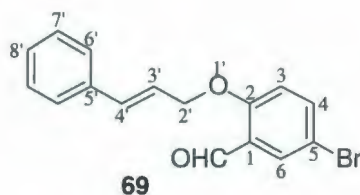
solvent was removed from the filtrate under reduced pressure and the residue was subjected to flash chromatography (10% ethyl acetate/hexanes) to afford **68** as a thick gum (0.77 g, 96%). δ_H(CDCl$_3$) = 10.49 (s, 1H), 7.42 (dd, J = 7.1, 2.5 Hz, 1H), 7.38-7.37 (m, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.3 Hz, 1H), 7.16-7.11 (m, 2H), 6.66 (d, J = 15.6 Hz, 1H), 6.43 (m, 1H), 4.82 (d, J = 6.4 Hz, 2H), 3.92 (s, 3H) ppm; δ_C(CDCl$_3$) = 190.5, 153.3, 151.4, 136.4, 134.6, 130.4, 128.8, 128.3, 126.8, 124.4, 119.4, 118.2, 75.3, 56.3 ppm (one carbon signal fewer than expected); MS m/z (relative intensity) = M$^+$ not observed, 251 (M$^+$-17, 100). HRMS [M$^+$] calcd for C$_{17}$H$_{16}$O$_3$ 268.1099 found 268.1108.

5-Bromo-2-(cinnamyloxy)benzaldehyde (69)

69

A mixture of 5-bromosalicylaldehyde **(67)** (0.10 g, 0.50 mmol), cinnamyl bromide (0.11 g, 0.53 mmol) **(44)** and anhydrous K$_2$CO$_3$ (0.073 g, 0.53 mmol) in acetone (5 mL) was heated at reflux for 5 h. The reaction mixture was allowed to cool to room temperature and then suction filtered through a pad of Celite® and the filter cake was washed with acetone. The solvent was removed from the filtrate under reduced pressure and the residue was subjected to flash chromatography (10% ethyl acetate/hexanes) to afford **69** as a pale yellow solid (0.15 g, 94%). mp = 69-71 °C; δ_H(CDCl$_3$) = 10.51 (s, 1H,

CHO), 7.66 (d, *J* = 2.3 Hz, 1H), 7.42-7.39 (m, 3H), 7.32-7.30 (m, 2H), 7.24 (dd, *J* = 7.4, 2.6 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 15.7 Hz, 1H), 6.45-6.41 (m, 1H), 4.69 (d, *J* = 6.5 Hz, 2H) ppm; δ_C(CDCl$_3$) = 190.7, 159.2, 136.7, 136.5, 133.8, 130.3, 128.4, 128.3, 127.9, 126.1, 124.4, 124.3, 114.2, 70.2 ppm; MS *m/z* (relative intensity) = M$^+$ not observed, 118 (100);. HRMS [M$^+$] calcd for C$_{16}$H$_{13}$BrO$_2$ 316.0099 found 316.0105.

(7a*R**, 13a*R**, 14*S**)-11-Methoxy-14-phenyl-5,6,7,7a,12,13,13a,14-octahydro-5,12-dioxa-7-azadibenzo[*a,h*]anthracen-6-one (70)

70
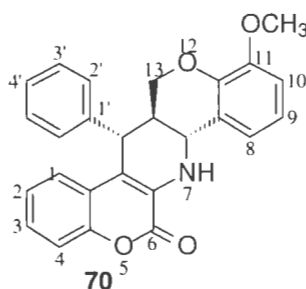
According to general procedure 3-A, 3-aminocoumarin (**25**) (0.040 g, 0.25 mmol), enal **68** (0.070, 0.26 mmol) and Yb(OTf)$_3$ (0.016 g, 10 mol%) afforded **70** as a white solid (0.092 g, 89%). mp = 261-262 °C; δ_H(CD$_2$Cl$_2$) = 7.30-7.27 (m, 3H), 7.26-7.24 (m, 1H), 7.22-7.19 (m, 3H), 7.01-6.96 (m, 4H), 6.88 (d, *J* = 6.9 Hz, 1H), 5.42 (s, 1H, H-7), 4.42-4.38 (m, 2H, H-7a, H-13α), 4.06 (t, *J* = 11.0 Hz, 1H, H-13β), 3.94 (d, *J* = 11.1 Hz, 1H, H-14), 3.79 (s, 3H, C-11-O*CH$_3$*), 2.41-2.35 (m, 1H, H-13a) ppm; δ_C(CD$_2$Cl$_2$) = 159.3 (C-6), 149.23, 149.21, 144.2, 142.6, 132.4, 129.6, 128.7, 127.8, 126.8, 124.9, 124.4, 122.3, 121.3, 121.1, 121.0, 117.2, 116.9, 111.7, 67.2 (C-13), 56.4 (C-11-O*CH$_3$*),

52.2 (C-7a), 45.1 (C-13a), 44.2 (C-14) ppm; IR ν = 3396 (w), 1717 (s), 1616 (w), 1598 (w), 1580 (w), 1494 (m), 1483 (m), 1457 (m), 1442 (m), 1342 (m), 1269 (m), 1216 (m), 1198 (m), 1181 (m), 1130 (m), 1115 (w), 1091 (m), 1063 (m) cm^{-1}; MS *m/z* (relative intensity) = 413 (M$^+$+2, 24), 412 (M$^+$+1, 97), 411 (42), 410 (100); HRMS [M$^+$] calcd for $C_{26}H_{21}NO_4$ 411.1471 found 411.1461.
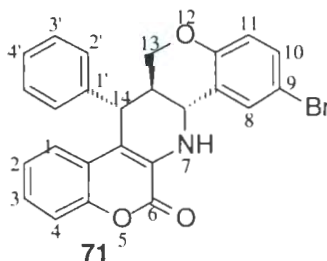
(7a*R**, 13a*R**, 14*S**)-9-Bromo-14-phenyl-5,6,7,7a,12,13,13a,14-octahydro-5,12-dioxa-7-azadibenzo[*a,h*]anthracen-6-one (71)

According to general procedure 3-A, 3-aminocoumarin (**25**) (0.040 g, 0.25 mmol), enal **69** (0.082, 0.26 mmol) and Yb(OTf)$_3$ (0.016 g, 10 mol%) afforded **71** as a white solid 0.10 g, 89%). mp = 271-272 °C; δ_H(CDCl$_3$) = 7.51 (s, 1H), 7.32-7.23 (m, 5H), 7.19-7.13 (m, 3H), 6.97-6.90 (m, 2H), 6.71 (d, 1H, *J* = 8.8 Hz), 5.41 (s, 1H, H-7), 4.44-4.33 (m, 2H, H-7a, H-13α), 4.05 (t, *J* = 10.7 Hz, 1H, H-13β), 3.90 (d, *J* = 10.6 Hz, 1H, H-14), 2.40-2.11 (m, 1H, H-13a) ppm; δ_C(CDCl$_3$) = 159.0 (C-6), 153.1, 148.7, 141.7, 132.2, 131.4, 129.4, 128.0, 127.6, 126.7, 124.5, 124.2, 123.0, 121.2, 120.2, 119.0, 116.6, 113.1, 66.7 (C-13), 51.4 (C-7a), 44.2 (C-13a), 43.8 (C-14) ppm (one carbon signal fewer

than expected); IR ν = 3357 (w), 1720 (s), 1630 (m), 1602 (w), 1501 (m), 1484 (m), 1461 (m), 1451 (s), 1404 (w), 1367 (m), 1322 (m), 1292 (w), 1256 (m), 1234 (m), 1198 (s), 1176 (m), 1137 (w), 1116 (w), 1091 (w), 1072 (w), 1047 (m), 1034 (s) cm^{-1}; MS m/z (GC/MS) (relative intensity) = 461 (M$^{+(81)}$, 94), 459 (M$^{+(79)}$, 100); HRMS [M$^+$] calcd for $C_{25}H_{18}BrNO_3$ 459.0470 found 459.0476.

(7aR*, 13aR*, 14S*)-11-Methoxy-2-methyl-14-phenyl-5,6,7,7a,12,13,13a,14-octahydro-5,12-dioxa-7-azadibenzo[a,h]anthracen-6-one (72)
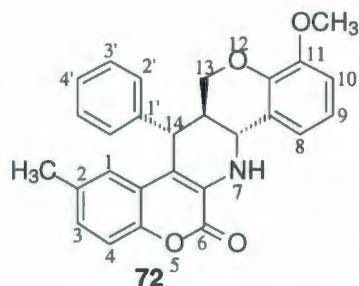
According to general procedure 3-A, 3-amino-6-methylcoumarin (0.044 g, 0.25 mmol), enal **68** (0.070 g, 0.26 mmol) and Yb(OTf)$_3$ (0.016 g, 10 mol%) afforded **72** as a white solid (0.089 g, 84%). mp = 230-232 °C; δ_H(CD$_2$Cl$_2$) = 7.24 (t , J = 7.0 Hz, 2H), 7.18 (d, J = 6.8 Hz, 1H), 7.14-7.13 (m, 2H), 7.06 (d, J = 8.4 Hz, 1H), 6.94-6.87 (m, 3H), 6.77 (d, J = 7.8 Hz, 1H), 6.73 (s, 1H), 5.32 (s, 1H, H-7), 4.33 (dd, J = 11.3, 3.5 Hz, 1H, H-13α), 4.30 (d, J = 10.9 Hz, 1H, H-7a), 3.98 (t, J = 11.5 Hz, 1H, H-13β), 3.84 (d, J = 10.8 Hz, 1H, H-14), 3.72 (s, 3H, C-11-OCH_3), 2.31 (m, 1H, H-13a), 2.00 (s, 3H, C-2-

CH_3) ppm; $\delta_C(CD_2Cl_2)$ = 159.5 (C-6), 149.2, 147.3, 144.2, 142.7, 134.0, 132.3, 129.6, 128.7, 127.8, 125.1, 122.4, 121.5, 121.1, 120.6, 117.2, 116.5, 111.7 (C-10), 67.2 (C-13), 56.4 (C-11-OCH_3), 52.1 (C-7a), 44.8 (C-13a), 44.1 (C-14), 28.6 (C-2-CH_3) ppm (one carbon signal fewer than expected); IR ν = 3358 (w), 1701 (s), 1678 (w), 1650 (w), 1613 (m), 1501 (s), 1469 (m), 1345 (w), 1312 (w), 1281 (w), 1252 (m), 1219 (m), 1191 (m), 1172 (w), 1119 (m), 1065 (w), 1033 (m) cm^{-1}; MS m/z (relative intensity) = 427 (M$^+$+2, 30), 426 (M$^+$+1, 100), 425 (18), 424 (32), 422 (11); HRMS [M$^+$] calcd for $C_{27}H_{23}NO_4$ 425.1627, found 425.1623.
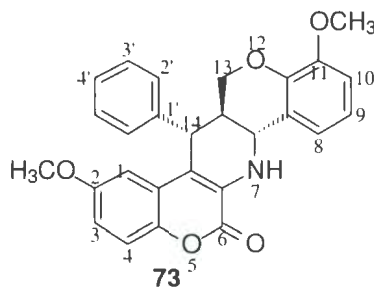
(7aR*, 13aR*, 14S*)-2,11-Dimethoxy-14-phenyl-5,6,7,7a,12,13,13a,14-octahydro-5,12-dioxa-7-azadibenzo[a,h]anthracen-6-one (73)

According to general procedure 3-A, 3-amino-6-methoxycoumarin (0.048 g, 0.25 mmol), enal **68** (0.070, 0.26 mmol) and Yb(OTf)$_3$ (0.016 g, 10 mol%) afforded **73** as a white solid (0.094, 85%). mp = 258-260 °C; $\delta_H(CD_2Cl_2)$ = 7.25 (t, J = 7.4 Hz, 2H), 7.19 (d, J = 7.4 Hz, 1H, H-4), 7.09-7.08 (m, 2H), 7.08 (d, J = 9.1 Hz, 1H), 6.93-6.87 (m, 2H), 6.76 (d, J = 7.7 Hz, 1H, H-10), 6.64 (dd, J = 9.0, 3.1 Hz, 1H, H-3), 6.34 (d, J = 2.9 Hz,

1H, H-1), 5.37 (s, 1H, H-7), 4.34-4.30 (m, 2H, H-7a, H-13α), 3.97 (t, J = 11.1 Hz, 1H, H-13β), 3.83 (d, J = 10.2 Hz, 1H, H-14), 3.71 (s, 3H, C-11-OCH_3), 3.33 (s, 3H, C-2-OCH_3), 2.32 (m, 1H, H-13a) ppm; δ_C(CD$_2$Cl$_2$) = 159.3 (C-6), 156.2, 149.2, 144.2, 143.5, 142.7, 132.5, 129.7, 128.7 (C-4), 127.9, 122.3, 121.5, 121.1, 120.8, 117.6, 117.2, 114.3 (C-3), 111.7 (C-10), 107.9 (C-1), 67.2 (C-13), 56.4 (C-11-OCH_3), 55.9 (C-2-OCH_3), 52.1 (H-7a), 44.7 (H-13a), 44.4 (H-14) ppm; IR v = 3365 (w), 1699 (s), 1619 (w), 1555 (m), 1501 (m), 1468 (w), 1421 (m), 1329 (m), 1302 (w), 1285 (w), 1257 (w), 1232 (m), 1182 (m), 1169 (m), 1029 (m) cm^{-1}; MS m/z (relative intensity) = 443 (M$^+$+2, 32), 442 (M$^+$+1, 100), 441 (24), 440 (48), 438 (26); HRMS [M$^+$] calcd for C$_{27}$H$_{23}$NO$_5$ 441.1576, found 441.1577.
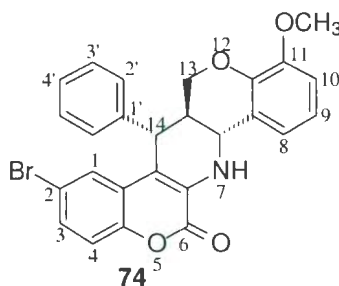
(7aR^*, 13aR^*, 14S^*)-2-Bromo-11-methoxy-14-phenyl-5,6,7,7a,12,13,13a,14-octahydro-5,12-dioxa-7-azadibenzo[a,h]anthracen-6-one (74)

According to general procedure 3-A, 3-amino-6-bromocoumarin (0.060 g, 0.25 mmol), enal **68** (0.070, 0.26 mmol) and Yb(OTf)$_3$ (0.016 g, 10 mol%) afforded **74** as an

off-white solid (0.092, 75%). mp = 253-255 °C; δ_H(CD$_2$Cl$_2$) = 7.28-7.26 (m, 2H), 7.22

(m, 1H), 7.17 (dd, J = 9.2, 1.8 Hz, 1H, H-3), 7.13 (m, 2H), 7.07 (d, J = 8.1 Hz, 1H, H-4),

7.02 (d, J = 2.1 Hz, 1H, H-1), 6.93-6.88 (m, 2H), 6.78 (d, J = 7.4 Hz, 1H, H-10), 5.44 (s,

1H, H-7), 4.35 (d, J = 11.5 Hz, 1H, H-7a), 4.31 (dd, J = 10.9 Hz, J = 3.9 Hz, 1H, H-13α),

3.97 (t, J = 11.3 Hz, 1H, H-13β), 3.80 (d, J = 11.1 Hz, 1H, H-14), 3.72 (s, 3H, C-11-

OCH_3), 2.31 (m, 1H, H-13a) ppm; δ_C(CD$_2$Cl$_2$) = 158.7 (C-6), 149.3, 148.0, 142.2, 141.9,

132.8, 129.8, 129.3 (C-3), 128.1, 127.5 (C-1), 122.9, 122.0, 121.2, 119.4, 118.5 (C-4),

117.2, 117.1, 111.8 (C-10), 67.2 (C-13), 56.4 (C-11-OCH_3), 52.1 (C-7a), 44.8 (C-13a),

44.1 (C-14) ppm (one carbon signal fewer than expected); IR ν = 3351 (m), 1710 (s),

1614 (w), 1584 (w), 1497 (m), 1482 (s), 1455 (m), 1407 (w), 1345 (m), 1316 (w), 1263

(s), 1229 (s), 1214 (m), 1203 (m), 1122 (w), 1091 (w), 1077 (w), 1059 (w), 1037 (s) cm^{-1};

HRMS [M$^+$] calcd for C$_{26}$H$_{20}$BrNO$_4$ 489.0576, found 489.0574.

(7aR*, 13aR*, 14S*)-11-Methoxy-2-nitro-14-phenyl-5,6,7,7a,12,13,13a,14-octahydro-

5,12-dioxa-7-azadibenzo[a,h]anthracen-6-one (75)
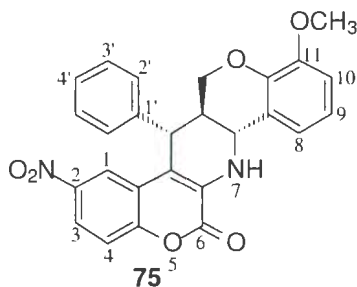
According to general procedure 3-A, 3-amino-6-nitrocoumarin (0.052 g, 0.25 mmol), enal **68** (0.070 g, 0.26 mmol) and Yb(OTf)$_3$ (0.016 g, 10 mol%) afforded **75** as a pale yellow solid (0.089, 78%). mp = 257-259 °C; δ_H(CD$_2$Cl$_2$) = 7.89 (dd, J = 8.7, 2.3 Hz, 1H), 7.82 (d, J = 2.7 Hz, 1H), 7.29-7.26 (m, 3H), 7.21-7.19 (m, 3H), 6.93-6.89 (m, 2H), 6.78 (dd, J = 7.2, 1.5 Hz, 1H), 5.53 (s, 1H, H-7), 4.41 (d, J = 10.7 Hz, 1H, H-7a), 4.31 (dd, J = 10.7 Hz, 3.2 Hz, 1H, H-13α), 3.98 (t, J = 11.5 Hz, 1H, H-13β), 3.90 (d, J = 11.3 Hz, 1H, H-14), 3.72 (s, 3H, C-11-*OCH$_3$*), 2.36 (m, 1H, H-13a) ppm; δ_C(CD$_2$Cl$_2$) = 163.2 (C-6), 158.1, 152.4, 149.3, 144.5, 144.3, 141.4, 133.2, 130.0, 128.3, 121.74, 121.67, 121.4, 121.3, 120.7, 119.2, 117.8, 117.0, 111.9, 67.1 (C-13), 56.5 (C-11-OCH$_3$), 52.1 (C-7a), 44.5 (C-13a), 44.1 (C-14) ppm; IR ν = 3395 (w), 1725 (s), 1629 (m), 1560 (m), 1499 (m), 1467 (w), 1451 (w), 1426 (w), 1343 (m), 1319 (w), 1282 (w), 1258 (w), 1234 (w), 1187 (m), 1170 (m), 1050 (m) cm^{-1}; MS m/z (relative intensity) = 457 (M$^+$+1, 14), 456 (M$^+$, 52), 455 (100), 419 (26), 214 (56); HRMS [M$^+$] calcd for C$_{26}$H$_{20}$N$_2$O$_6$ 456.1321 found 456.1325.

(7a*R**, 13a*R**, 14*S**)-4,11-Dimethoxy-14-phenyl-5,6,7,7a,12,13,13a,14-octahydro-5,12-dioxa-7-azadibenzo[*a,h*]anthracen-6-one (76)
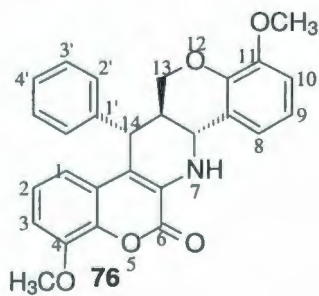
According to general procedure 3-A, 3-amino-8-methoxycoumarin (0.048 g, 0.25 mmol), enal **68** (0.070 g, 0.26 mmol) and Yb(OTf)$_3$ (0.016 g, 10 mol%) afforded **76** as an off-white solid (0.095, 86%). mp = 265-266 °C; δ_H(CD$_2$Cl$_2$) = 7.31-7.29 (m, 2H), 7.26-7.23 (m, 1H), 7.19-7.18 (m, 2H), 7.01 (d, J = 7.8 Hz, 1H), 6.97 (t, J = 8.3 Hz, 1H), 6.87-6.84 (m, 2H), 6.77 (d, J = 7.5 Hz, 1H), 6.60 (d, J = 7.7 Hz, 1H), 5.43 (s, 1H, H-7), 4.41-4.37 (m, 2H, H-7a, H-13α), 4.05 (t, J = 11.0 Hz, 1H, H-13β), 3.92-3.91 (m, 4H, H-14), 3.79 (s, 3H), 2.36 (m, 1H, H-13a) ppm; δ_C(CD$_2$Cl$_2$) = 158.8, 149.2, 147.8, 144.2, 142.8, 138.7, 132.5, 129.6, 128.6, 127.7, 124.0, 122.3, 121.8, 121.5, 121.1, 117.2, 116.7, 111.7, 109.3, 67.1, 56.7, 56.4, 52.1, 45.1, 44.3 ppm; IR v = 3345 (m), 1681 (s), 1602 (w), 1576 (m), 1558 (w), 1483 (m), 1439 (m), 1337 (m), 1258 (m), 1205 (s), 1175 (s), 1133 (m), 1109 (m), 1090 (m), 1064 (s) cm^{-1}; MS m/z (relative intensity) = 443 (M$^+$+2, 32), 442 (M$^+$+1, 100), 440 (12); HRMS [M$^+$] calcd for C$_{27}$H$_{23}$NO$_5$ 441.1576 found 441.1583.

**4-Acetyl-1-cinnamyl 1H-pyrrole-2-carbaldehyde (78)**

78
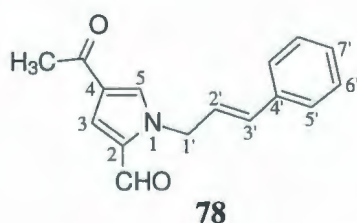
To a clear yellow solution of **77** (0.14 g, 1.0 mmol) in freshly distilled DMF (2.0 mL) was added sodium hydride (60% dispersion in mineral oil, 0.044 g, 1.1 mmol) at 0 °C followed by the addition of cinnamyl bromide (0.22 g, 1.1 mmol). The resulting turbid orange mixture was stirred at rt for 1 h. The reaction was quenched by the addition

of few drops of methanol. Ice-cold water was then added and the mixture was suction filtered. The solids were washed with cold 5% ethyl acetate/hexanes to afford **78** as a pale yellow solid (0.12 g, 46%). The filtrate was diluted with water and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water, washed with brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting yellow residue was subjected to flash chromatography (15% ethyl acetate/hexanes) to afford **78** as a pale yellow solid (0.046 g, 18%). mp = 161-162 °C. δ_H(CDCl$_3$) = 9.63 (s, 1H, *CHO*), 7.59 (s, 1H), 7.36-7.35 (m, 3H), 7.32-7.29 (m, 2H), 7.25 (m, 1H), 6.54 (d, J = 15.7 Hz, 1H, H-3′), 6.30 (ddd, J = 15.9, 12.6, 3.2 Hz, 1H, H-2′), 5.13 (d, J = 6.2 Hz, 2H, H-1′), 2.44 (s, 3H, *COCH₃*) ppm; δ_C(CDCl$_3$) = 192.7 (*CHO*), 180.3 (*COCH₃*), 135.9, 134.4, 133.0, 132.2, 128.8, 128.4, 126.8, 126.4, 124.2, 123.7, 51.4 (C-1′), 27.4 (*COCH₃*) ppm; MS *m/z* (relative intensity) = 254 (M$^+$+1, 100), 211 (65); HRMS [M$^+$] calcd for C$_{16}$H$_{15}$NO$_2$ 253.2958 found 253.2964.

(7a*S**, 11a*S**, 12*R**)-9-Acetyl-12-phenyl-7,7a,10a,11,11a,12-hexahydro-6*H*-chromeno[3,4-*b*]pyrrolizino[2,1-*e*]pyridin-6-one (79)

79
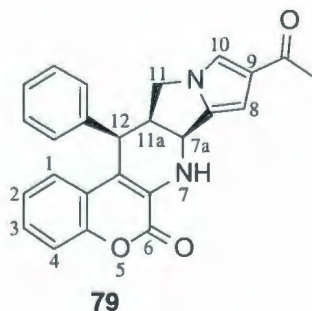
According to general procedure 3-A, 3-aminocoumarin (**25**) (0.040 g, 0.25 mmol), enal **78** (0.066 g, 0.26 mmol) and Yb(OTf)$_3$ (0.016 g, 10 mol%) were reacted at rt for 6 h and then heated at reflux for 18 h. The precipitate was suction filtered and the solids were washed with cold acetonitrile to afford **79** as a pale yellow solid (0.038 g, 38%). The solvent was removed from filtrate under reduced pressure and the residue was subjected to flash chromatography (30% ethyl acetate/hexanes) to afford **79** as a pale yellow solid (0.011 g, 11%). Combined yield = 0.049 g, 49%. mp = 265-266 °C; δ_H(CDCl$_3$) = 7.36-7.33 (m, 4H), 7.30-7.26 (m, 2H), 7.24 (s, 1H), 7.22-7.18 (m, 2H), 7.12-7.08 (m, 1H), 6.47 (s, 1H), 4.93 (s, 1H, H-7), 4.65 (d, J = 5.4 Hz, 1H, H-7a), 4.30 (s, 1H, H-12), 4.23 (dd, J = 10.8, 7.4 Hz, 1H, H-11α), 3.84 (t, J = 10.8 Hz, 1H, H-11β), 3.40-3.35 (m, 1H, H-11a), 2.35 (s, 3H, CO*CH$_3$*) ppm; δ_C(CDCl$_3$) = 193.4 (*CO*CH$_3$), 158.2 (C-6), 148.0, 142.5, 138.7, 129.8, 129.5, 128.5, 127.8, 127.5, 126.2, 124.9, 121.6, 120.8, 116.7, 112.0, 102.3, 50.1 (C-11), 49.4 (C-11a), 46.7 (C-7a), 38.9 (C-12), 27.2 (CO*CH$_3$*) ppm; MS *m/z* (relative intensity) = 400 (M$^+$+2, 21), 399 (100); HRMS [M$^+$] calcd for C$_{25}$H$_{20}$N$_2$O$_3$ 396.1474 found 396.1479.

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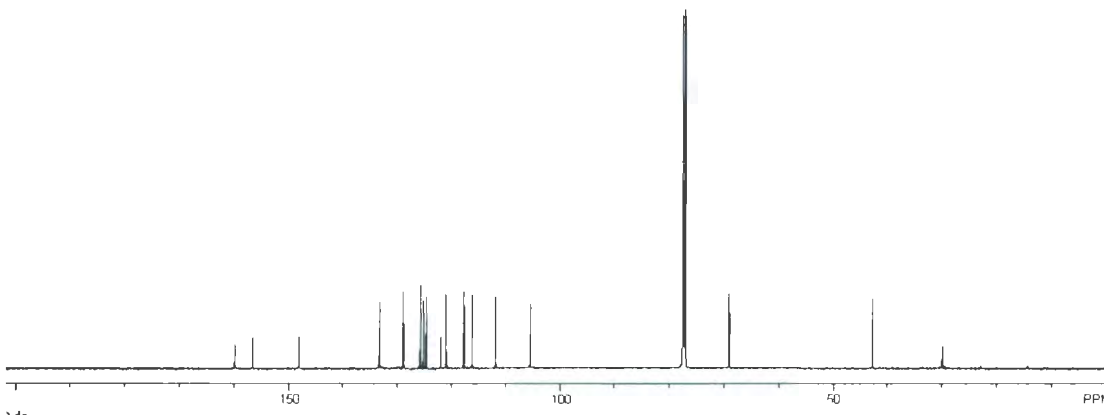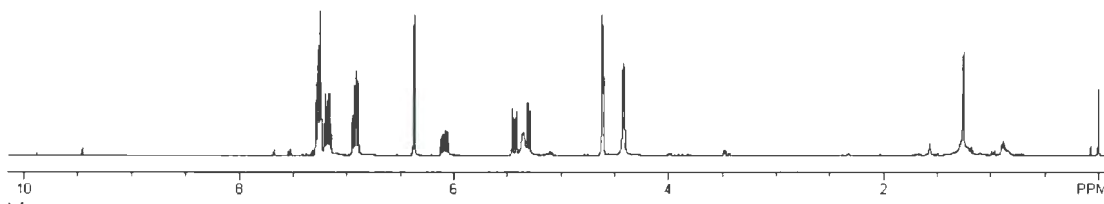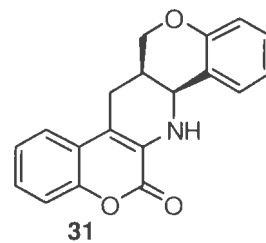
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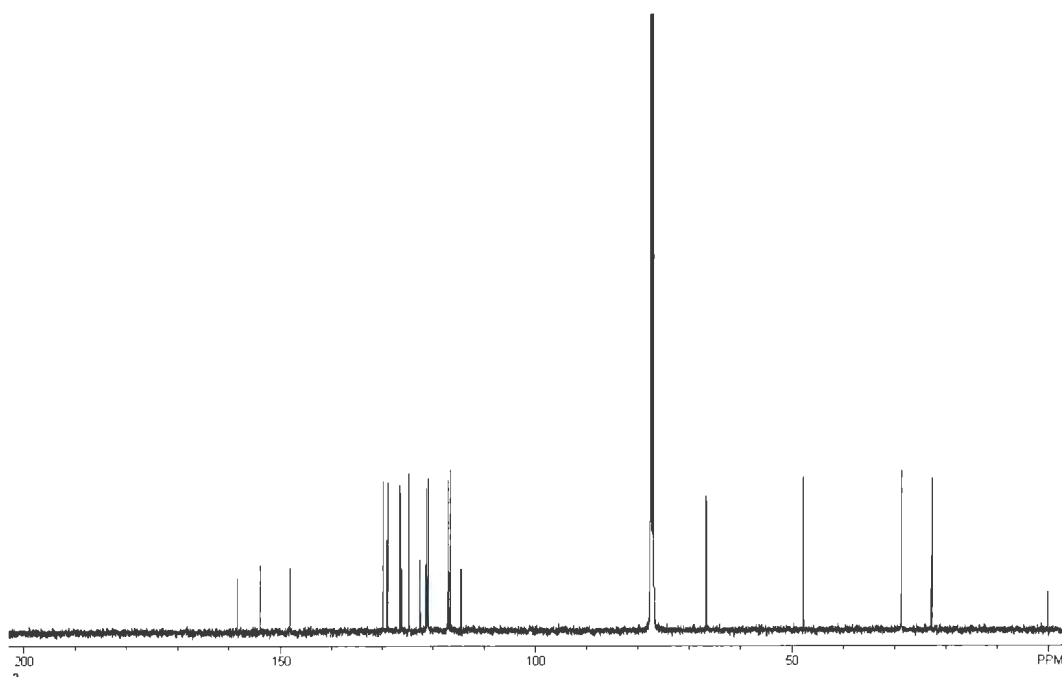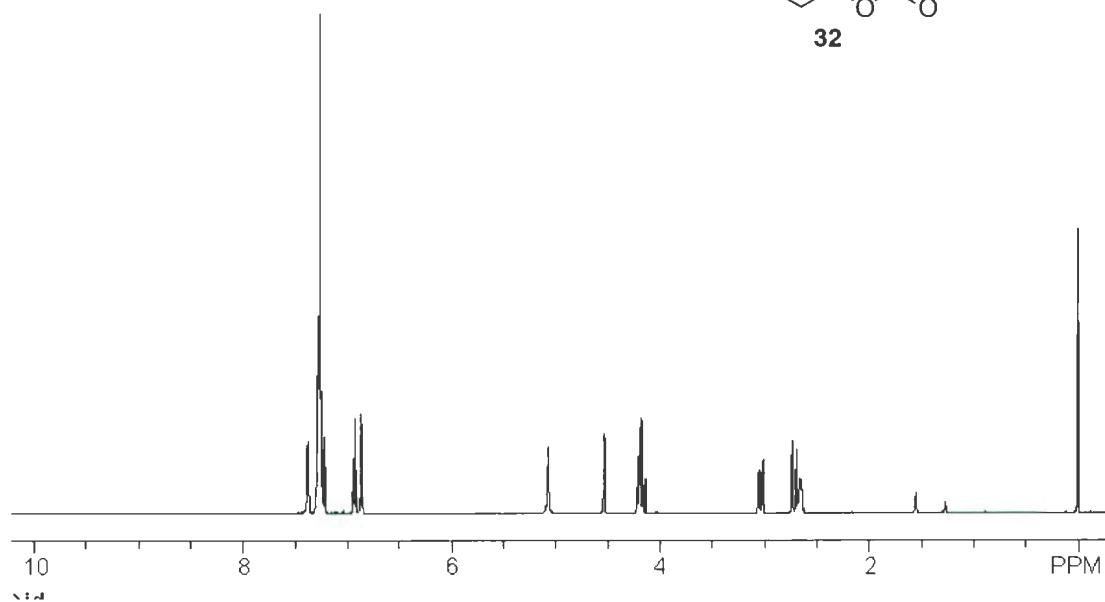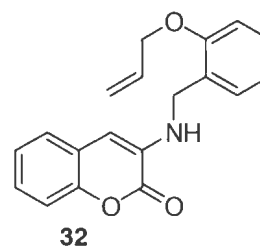
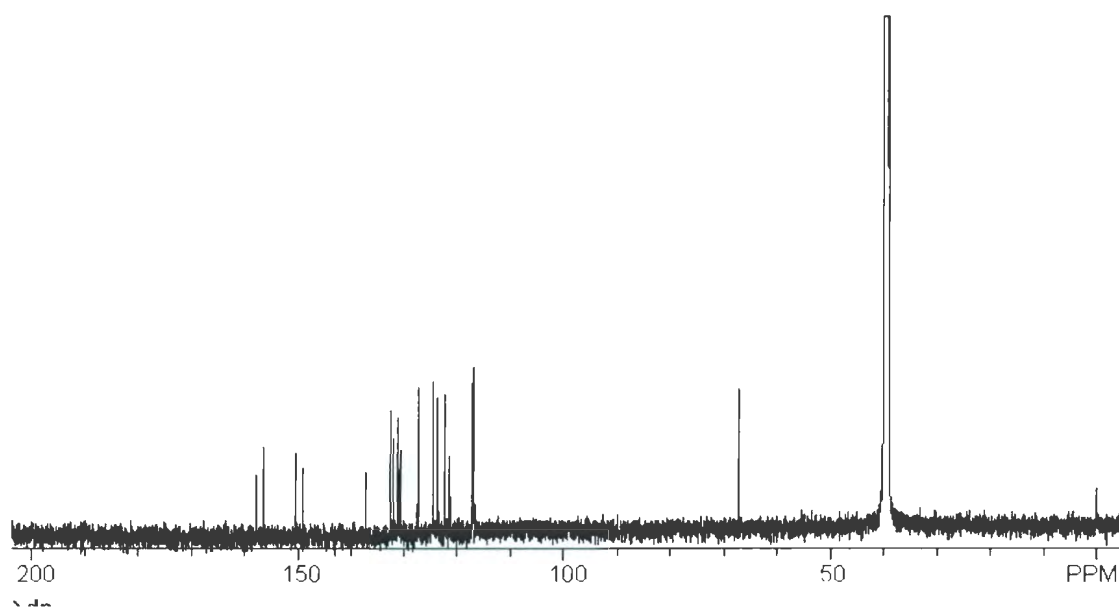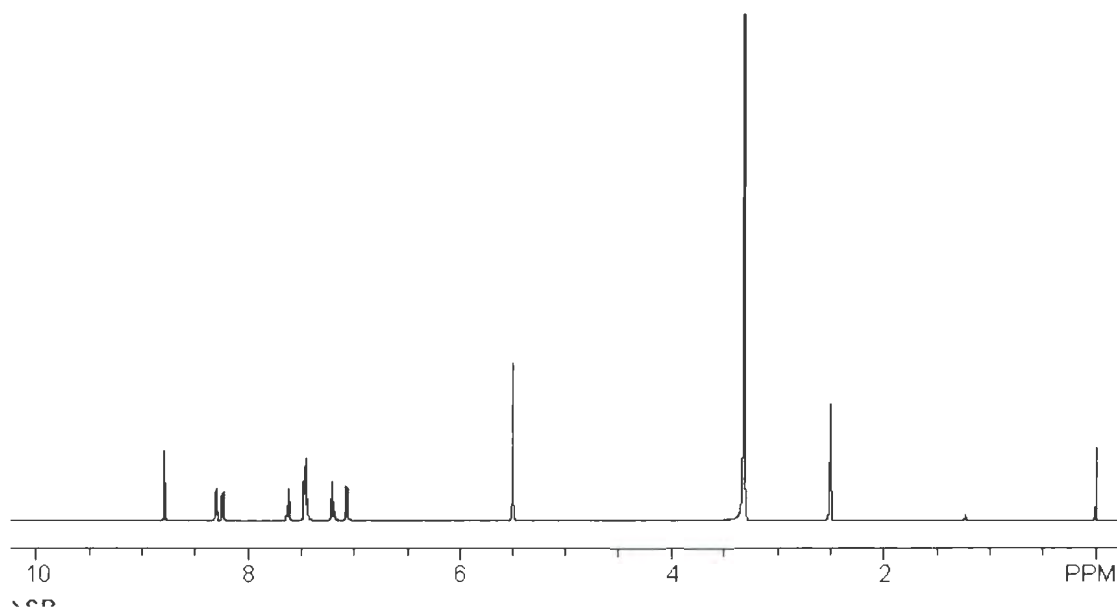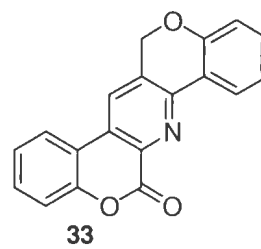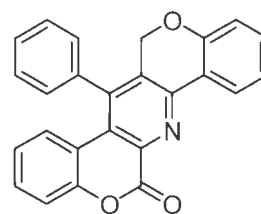27. Anderson, H. J.; Loader, C. E. Foster, A. *Can. J. Chem.* **1978**, *58*, 2527–2530.

3.6 Appendix

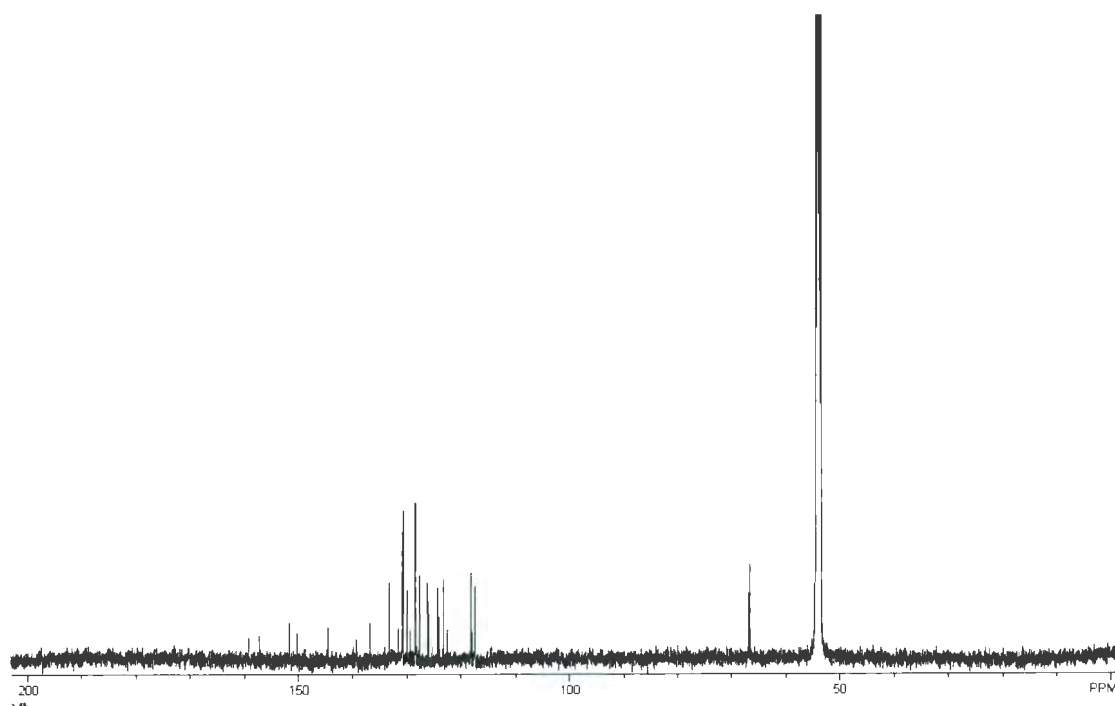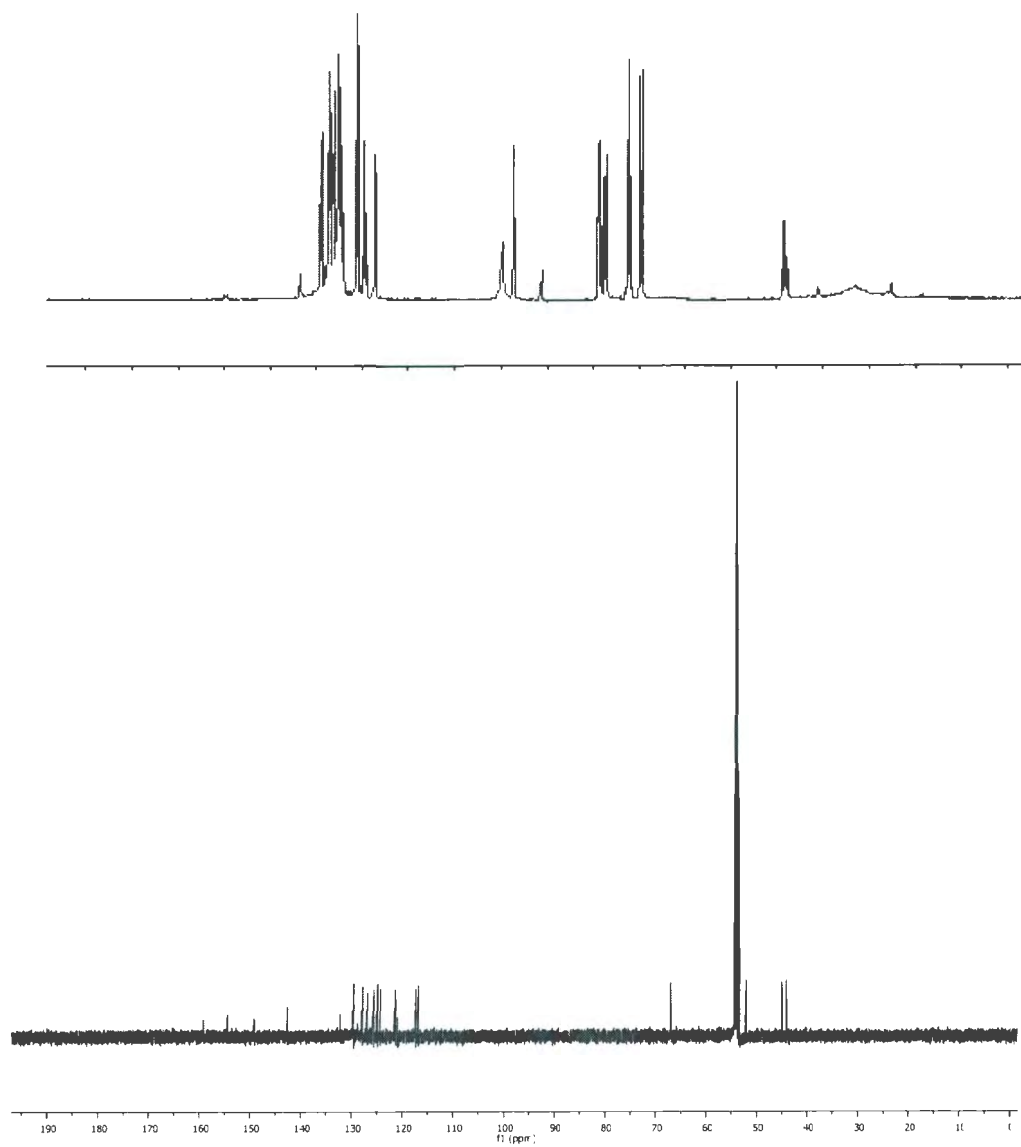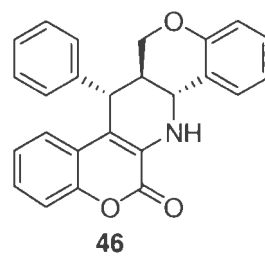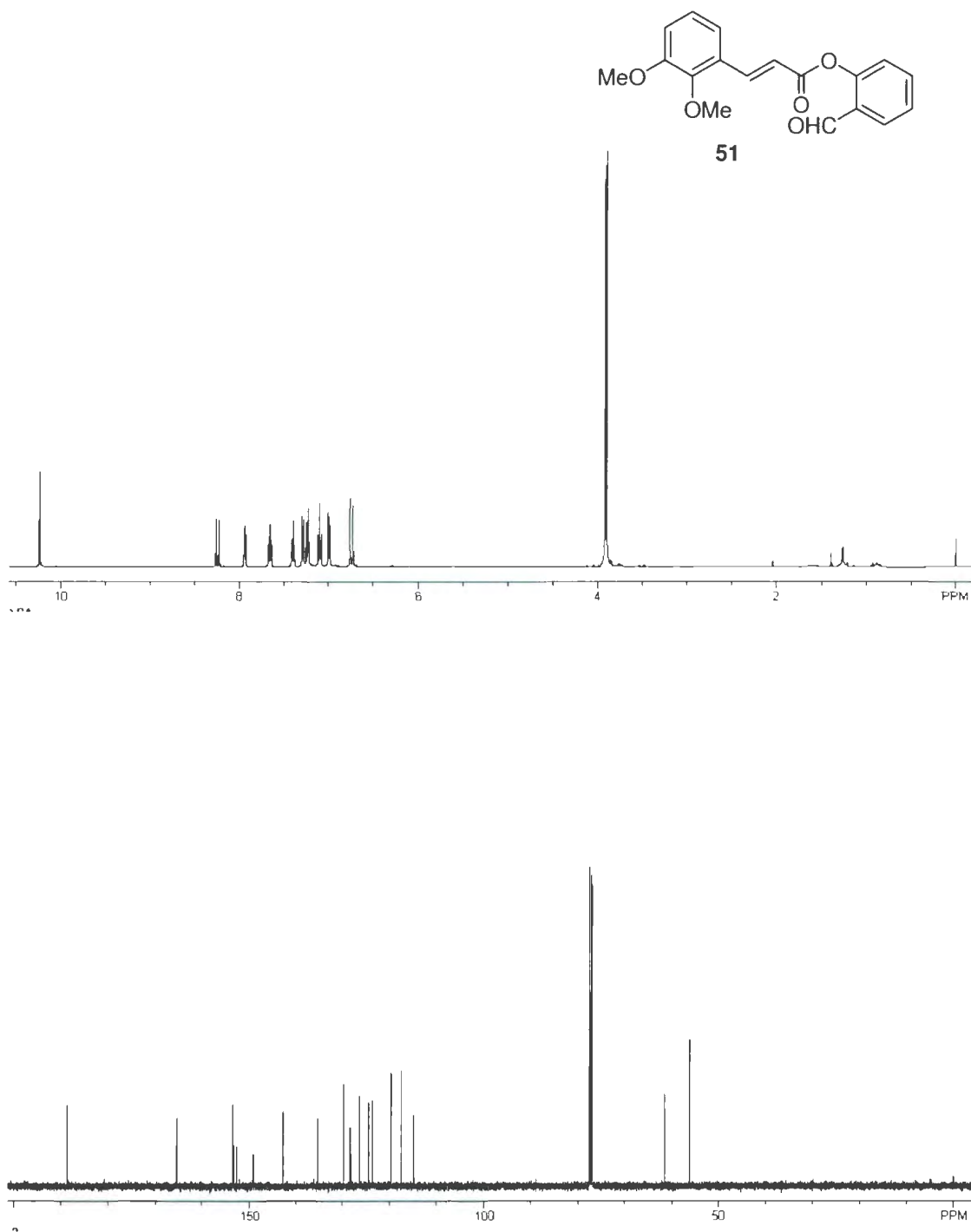## 3.6.1 ^{1}H and ^{13}C NMR Spectra for Selected Compounds

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51

55

56

57

58

60

61

62

10   8   6   4   2   0 PPM

63

64

68

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70

¹³C NMR peaks:
158.953, 153.146, 148.694, 141.693, 132.167, 131.419, 129.372, 128.036, 127.602, 126.713, 124.498, 124.173, 123.006, 121.214, 120.179, 119.006, 116.627, 113.145, 66.748, 51.470, 44.173, 43.757

¹H NMR peaks:
7.510, 7.321, 7.307, 7.300, 7.296, 7.292, 7.278, 7.264, 7.262, 7.246, 7.235, 7.233, 7.185, 7.181, 7.171, 7.167, 7.155, 7.151, 7.115, 6.967, 6.963, 6.951, 6.947, 6.929, 6.926, 6.915, 6.913, 6.899, 6.896, 6.719, 6.701, 5.405, 4.357, 4.351, 4.335, 4.330, 4.047, 4.027, 4.004, 3.910, 3.889, 2.399, 2.392, 2.378, 2.371, 2.354, 2.348, 2.334, 2.328, 2.114, 0.005

Integrations: 0.93, 2.72, 2.03, 4.06, 0.89, 1.00, 1.99, 1.03, 0.97, 0.91

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3.6.2 X-ray Crystal Structure Data for **58**

<u>Data Collection</u>

A colorless platelet crystal of $C_{25}H_{18}N_2O_5$ having approximate dimensions of 0.30 x 0.30 x 0.03 mm was mounted on a glass fiber. All measurements were made on a Rigaku Saturn CCD area detector with graphite monochromated Mo-Kα radiation.

Indexing was performed from 360 images that were exposed for 20 seconds. The crystal-to-detector distance was 35.04 mm.

Cell constants and an orientation matrix for data collection corresponded to a primitive monoclinic cell with dimensions:

$a = 8.7591(18)$ Å

$b = 13.493(3)$ Å $\qquad \beta = 100.732(5)^{o}$

$c = 16.814(4)$ Å

$V = 1952.5(7)$ Å^3

For Z = 4 and F.W. = 426.43, the calculated density is 1.451 g/cm^3. The systematic absences of:

h0l: h $\pm$ 2n

0k0: k $\pm$ 2n

uniquely determine the space group to be:

$$P2_1/a \ (\#14)$$

The data were collected at a temperature of -120 $\pm$ 1°C to a maximum 2θ value of 65.4^{o}. A total of 690 oscillation images were collected. A sweep of data was done using

ω scans from -75.0 to 105.0° in 0.5° step, at χ=0.0° and ϕ = 0.0°. The exposure rate was 40.0 [sec./$^\circ$]. The detector swing angle was 15.12°. A second sweep was performed using ω scans from -75.0 to 90.0° in 0.5° step, at χ=54.0° and ϕ = 90.0°. The exposure rate was 40.0 [sec./$^\circ$]. The detector swing angle was 15.12°. The crystal-to-detector distance was 35.04 mm. Readout was performed in the 0.137 mm pixel mode.

Data Reduction

Of the 17498 reflections that were collected, 3839 were unique (R_{int} = 0.062); equivalent reflections were merged. Data were collected and processed using CrystalClear (Rigaku). Net intensities and sigmas were derived as follows:

$$F^2 = [\Sigma(P_i - mB_{ave})] \cdot Lp^{-1}$$

where P_i is the value in counts of the ith pixel

m is the number of pixels in the integration area

B_{ave} is the background average

Lp is the Lorentz and polarization factor

$$B_{ave} = \Sigma(B_j)/n$$

where n is the number of pixels in the background area

B_j is the value of the jth pixel in counts

$$\sigma^2(F^2_{hkl}) = [(\Sigma P_i) + m((\Sigma(B_{ave} - B_j)^2)/(n-1))] \cdot Lp \cdot errmul + (erradd \cdot F^2)^2$$

where erradd = 0.00

errmul = 1.00

The linear absorption coefficient, μ, for Mo-Kα radiation is 1.024 cm^{-1}. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction[2] was applied (coefficient = 0.004120). A numerical absorption correction was applied which resulted in transmission factors ranging from 0.9784 to 0.9964.

Structure Solution and Refinement

The structure was solved by direct methods[3] and expanded using Fourier techniques[4]. The non-hydrogen atoms were refined anisotropically. Some hydrogen atoms were refined isotropically, some were refined using the riding model, and the rest were included in fixed positions. The final cycle of full-matrix least-squares refinement[5] on F^2 was based on 3822 observed reflections and 294 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.0939$$

$$wR2 = [\, \Sigma \, (\, w \, (Fo^2 - Fc^2)^2 \,) / \, \Sigma \, w(Fo^2)^2]^{1/2} = 0.1756$$

The standard deviation of an observation of unit weight[6] was 1.32. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.19 and -0.19 e$^-$/Å^3, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[7]. Anomalous dispersion effects were included in Fcalc[8]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[9]. The values for the mass attenuation coefficients are those of

Creagh and Hubbell[10]. All calculations were performed using the CrystalStructure[11,12] crystallographic software package except for refinement, which was performed using SHELXL-97[13].

References

(1) CrystalClear: Rigaku Corporation, 1999. CrystalClear Software User's Guide, Molecular Structure Corporation, (c) 2000.J.W.Pflugrath (1999) Acta Cryst. D55, 1718-1725.

(2) Larson, A.C. (1970), Crystallographic Computing, 291-294. F.R. Ahmed, ed. Munksgaard, Copenhagen (equation 22, with V replaced by the cell volume).

(3) SHELX97: Sheldrick, G.M. (1997).

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

(5) Least Squares function minimized: (SHELXL97)

$$\Sigma w(F_o^2-F_c^2)^2 \quad \text{where w = Least Squares weights.}$$

(6) 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

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

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Chemical Crystallography Laboratory, Oxford, UK. (1996)

(13) SHELX97: Sheldrick, G.M. (1997).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{25}H_{18}N_2O_5$
Formula Weight	426.43
Crystal Color, Habit	colorless, platelet
Crystal Dimensions	0.20 X 0.20 X 0.20 mm
Crystal System	monoclinic
Lattice Type	Primitive
Detector Position	35.04 mm
Pixel Size	0.137 mm
Lattice Parameters	$a = 8.7591(18)$ Å $b = 13.493(3)$ Å $c = 16.814(4)$ Å $\beta = 100.732(5)°$ $V = 1952.5(7)$ Å^3
Space Group	$P2_1/a$ (#14)
Z value	4
D_{calc}	1.451 g/cm^3
F_{000}	888.00
$\mu(MoK\alpha)$	1.024 cm^{-1}

B. Intensity Measurements

Detector	Rigaku Saturn
Goniometer	Rigaku AFC8
Radiation	MoKα (λ = 0.71070 Å) graphite monochromated
Detector Aperture	70 mm x 70 mm
Data Images	690 exposures
ω oscillation Range (χ=0.0, ϕ=0.0)	-75.0 - 105.0°
Exposure Rate	40.0 sec./$^\circ$
Detector Swing Angle	15.12°
ω oscillation Range (χ=54.0, ϕ=90.0)	-75.0 - 90.0°
Exposure Rate	40.0 sec./$^\circ$
Detector Swing Angle	15.12°
Detector Position	35.04 mm
Pixel Size	0.068 mm
$2\theta_{max}$	65.4°
No. of Reflections Measured	Total: 17498 Unique: 3822 (R_{int} = 0.062)
Corrections	Lorentz-polarization Secondary Extinction (coefficient: 4.12000e-003) Numerica Absorption (0.9964 – 0.9784)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma\, w\, (Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/[\,\sigma^2(Fo^2) + (0.0352 \cdot P)^2 + 1.5665 \cdot P\,]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$
$2\theta_{max}$ cutoff	52.0^o
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	3822
No. Variables	294
Reflection/Parameter Ratio	13.00
Residuals: R1 (I>2.00σ(I))	0.0939
Residuals: R (All reflections)	0.1091
Residuals: wR2 (All reflections)	0.1756
Goodness of Fit Indicator	1.319
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.19 e$^-$/Å^3
Minimum peak in Final Diff. Map	-0.19 e$^-$/Å^3

TABLE 3.4 Bond lengths (Å)

atom	atom	distance	atom	atom	distance
O(1)	C(1)	1.356(4)	O(1)	C(19)	1.395(4)
O(2)	C(1)	1.217(4)	O(3)	C(9)	1.371(4)
O(3)	C(10)	1.426(4)	O(4)	N(2)	1.217(5)
O(5)	N(2)	1.226(5)	N(1)	C(2)	1.381(4)
N(1)	C(3)	1.458(4)	N(2)	C(23)	1.474(5)
C(1)	C(2)	1.455(4)	C(2)	C(13)	1.357(4)
C(3)	C(4)	1.519(4)	C(3)	C(11)	1.523(4)
C(4)	C(5)	1.385(4)	C(4)	C(9)	1.389(5)
C(5)	C(6)	1.392(5)	C(6)	C(7)	1.378(5)
C(7)	C(8)	1.379(5)	C(8)	C(9)	1.389(5)
C(10)	C(11)	1.518(5)	C(11)	C(12)	1.541(4)
C(12)	C(13)	1.518(4)	C(12)	C(20)	1.529(4)
C(13)	C(14)	1.448(4)	C(14)	C(19)	1.393(5)
C(14)	C(15)	1.400(4)	C(15)	C(16)	1.370(5)
C(16)	C(17)	1.385(5)	C(17)	C(18)	1.378(5)
C(18)	C(19)	1.391(4)	C(20)	C(21)	1.387(4)
C(20)	C(25)	1.389(5)	C(21)	C(22)	1.386(5)
C(22)	C(23)	1.369(5)	C(23)	C(24)	1.381(5)
C(24)	C(25)	1.391(5)			

TABLE 3.5 Bond angles (º)

atom	atom	atom	angle	atom	atom	atom	angle
C(1)	O(1)	C(19)	120.8(3)	C(9)	O(3)	C(10)	117.6(3)
C(2)	N(1)	C(3)	114.3(3)	O(4)	N(2)	O(5)	123.5(4)
O(4)	N(2)	C(23)	119.2(4)	O(5)	N(2)	C(23)	117.3(4)
O(2)	C(1)	O(1)	117.5(3)	O(2)	C(1)	C(2)	123.8(3)
O(1)	C(1)	C(2)	118.7(3)	C(13)	C(2)	N(1)	124.6(3)
C(13)	C(2)	C(1)	121.6(3)	N(1)	C(2)	C(1)	113.8(3)
N(1)	C(3)	C(4)	112.0(3)	N(1)	C(3)	C(11)	107.0(3)
C(4)	C(3)	C(11)	110.0(3)	C(5)	C(4)	C(9)	118.2(3)
C(5)	C(4)	C(3)	122.4(2)	C(9)	C(4)	C(3)	119.5(3)

C(4)	C(5)	C(6)	121.5(2)	C(7)	C(6)	C(5)
119.2(3)						
C(6)	C(7)	C(8)	120.3(3)	C(7)	C(8)	C(9)
120.0(4)						
O(3)	C(9)	C(4)	123.7(3)	O(3)	C(9)	C(8)
115.6(3)						
C(4)	C(9)	C(8)	120.8(3)	O(3)	C(10)	C(11)
112.3(3)						
C(10)	C(11)	C(3)	108.3(3)	C(10)	C(11)	C(12)
112.4(3)						
C(3)	C(11)	C(12)	111.3(3)	C(13)	C(12)	C(20)
113.3(3)						
C(13)	C(12)	C(11)	111.0(3)	C(20)	C(12)	C(11)
108.6(3)						
C(2)	C(13)	C(14)	118.1(3)	C(2)	C(13)	C(12)
120.3(3)						
C(14)	C(13)	C(12)	121.6(3)	C(19)	C(14)	C(15)
115.6(3)						
C(19)	C(14)	C(13)	119.3(3)	C(15)	C(14	C(13
125.0(3)						
C(16)	C(15)	C(14)	121.7(3)	C(15)	C(16)	C(17)
120.6(3)						

C(18)	C(17)	C(16)	120.4(3)	C(17)	C(18)	C(19)
	117.6(3)					
C(18)	C(19)	C(14)	124.1(3)	C(18)	C(19)	O(1)
	115.0(3)					
C(14)	C(19)	O(1)	121.0(3)	C(21)	C(20)	C(25)
	119.0(3)					
C(21)	C(20)	C(12)	120.4(3)	C(25)	C(20)	C(12)
	120.5(3)					
C(22)	C(21)	C(20)	121.3(3)	C(23)	C(22)	C(21)
	117.9(3)					
C(22)	C(23)	C(24)	123.2(3)	C(22)	C(23)	N(2)
	118.0(4)					
C(24)	C(23)	N(2)	118.8(4)	C(23)	C(24)	C(25)
	117.7(4)					
C(20)	C(25)	C(24)	120.9(3)			

Chapter 4. Toward the Synthesis of a

Coum[5]isophenacene

4.1 Introduction

Due to the general curiosity regarding reactivity and potential applications in optoelectronic devices, linearly-fused polycyclic aromatic compounds have become the subject of great interest as fundamental skeletons for functional organic molecules.[1] Linear polynuclear hydrocarbons, which are also called [n]acenes, have received considerable attention in this regard. Pentacene (1) (Fig. 4.1), which has five linearly-fused benzene rings, is by far the most thoroughly studied and a promising candidate for organic thin-film transistors.[2] Recent research in this field has resulted in the synthesis of various π-conjugated systems including higher acene homologs such as 3 (Scheme 4.1),[3] heteroacenes such as 4[4] and main group element-containing π-conjugated (acene-like) molecules such as 5 (Fig. 4.2).[5] Within the heteroacene class, various heterocyclic motifs have been investigated.[6]

1
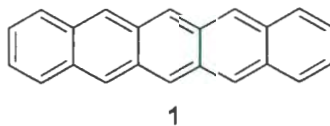
FIGURE 4.1 Pentacene **1**

SCHEME 4.1 Synthesis of a Functionalized Heptacene Derivative **3**
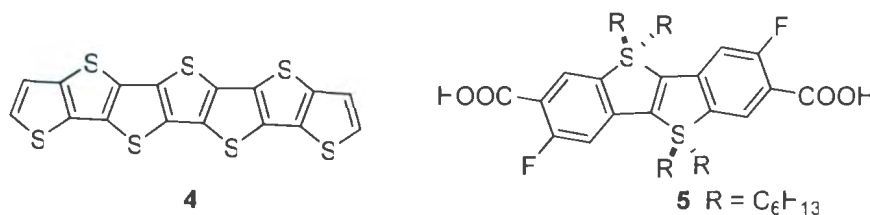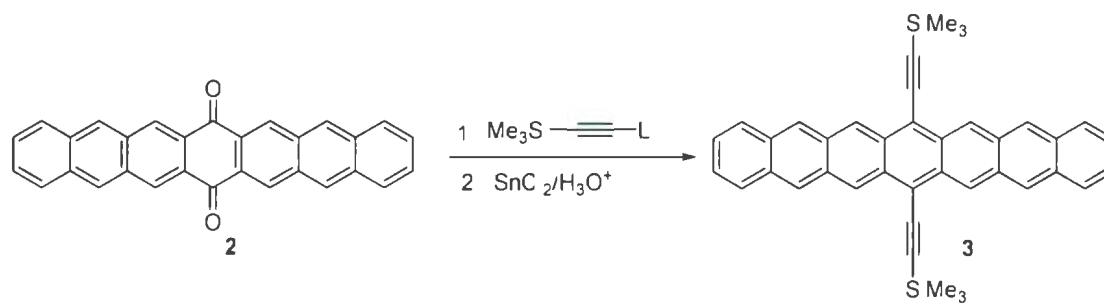
FIGURE 4.2 Heptathienoacene **4** and Silicon-based Heteroacene **5**

In connection with the involvement of the Bodwell group in the development of new electron deficient dienes for application in the inverse electron demand Diels-Alder (IEDDA) reactions, chromone-fused dienes **6** (EWG = electron withdrawing group) have been prepared.[7] These dienes were utilized in the synthesis of xanthone derivatives by reaction with various electron rich alkenes, *e.g.* enamine **7** (Scheme 4.2). This xanthone-building strategy was recently applied to the synthesis of a heteroacene **12**, which contains an alternating 4*H*-pyran-4-one / benzene motif (Scheme 4.3).[8] Work aimed at the synthesis of more ambitious targets such as **13** (Fig. 4.3) has also been initiated.

SCHEME 4.2 Synthesis of Xanthones by IEDDA Methodology
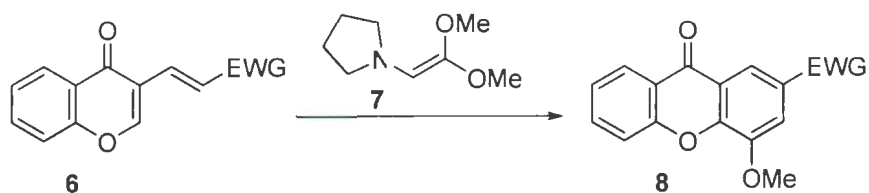
SCHEME 4.3 Application of IEDDA Chemistry to the Synthesis of a Hetero[5]acene **12**
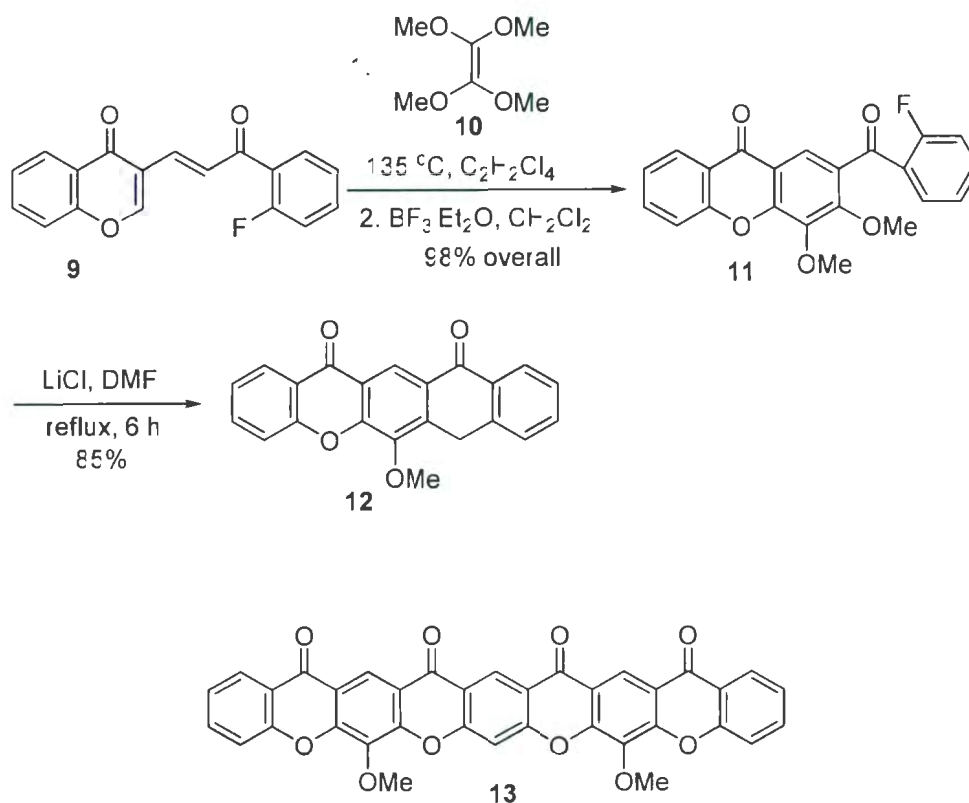
FIGURE 4.3 A Hetero[9]acene of Current Synthetic Interest in the Bodwell Group

The [*n*]phenacenes, *e.g.* [9]phenacene (**14**) (Fig. 4.4), are isomeric to the [*n*]acenes and have received considerable attention in recent years.[9] However,

heteroaromatic analogs of [n]phenacenes have received considerably less attention.[10] Another PAH motif, which is isomeric to the [n]phenacenes and shares an oligo(p-phenylene) backbone is exemplified by compound **15** (Fig. 4.4), which has no trivial name and will be referred to as "isophenacenes" in this thesis. Very little work has been invested in studying this class of compounds, for both the parent systems[11] and heteroaromatic analogs.[12]

14　　　　　　　　**15**
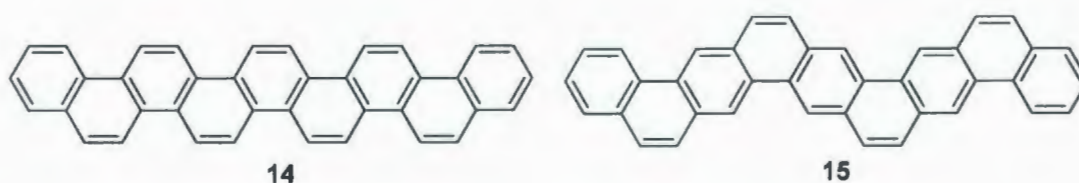
FIGURE 4.4 [9]Phenacene (**14**) and [9]Isophenacene (**15**)

As is the case with [n]phenacenes, [n]isophenacenes can be viewed as graphite ribbons of varying lengths. In this case, the ribbons have a serpentine motif. Alternatively, this class of compounds may also be viewed as oligo(p-phenylene) derivatives fused with benzene rings alternately on either side of the p-phenylene backbone. Although this motif appears to be interesting in view of its potential electronic and optical properties, most of the synthetic work appears to be limited to smaller members of this class ($n = 5$).[11]

Compound **18** is systematically named as dibenzo[a,h]anthracene, but will be referred to here as [5]isophenacene (due to the presence of five benzene rings). It has been synthesized using several different approaches.[11] Recently, ring-closing metathesis

310

of tetraene **16** and intramolecular benzannulation of diyne **19** were used by King[11a] and Liu,[11b] respectively, for the efficient synthesis of **18** (Scheme 4.4). Heteroaromatic analogs[12] of these type of compounds will be referred to as hetero[*n*]isophenacenes, where *n* represents the number of aromatic rings. Nitrogen-containing analogs of [5]isophenacene have also been prepared.[12] For example, dibenzo[*a*,*h*]phenazine (**22**) was prepared from 1-aminonaphthalene (**20**) and 1-nitronaphthalene (**21**) through the action of ethylmagnesium bromide (Scheme 4.5).[12a]

SCHEME 4.4 Synthesis of **18**
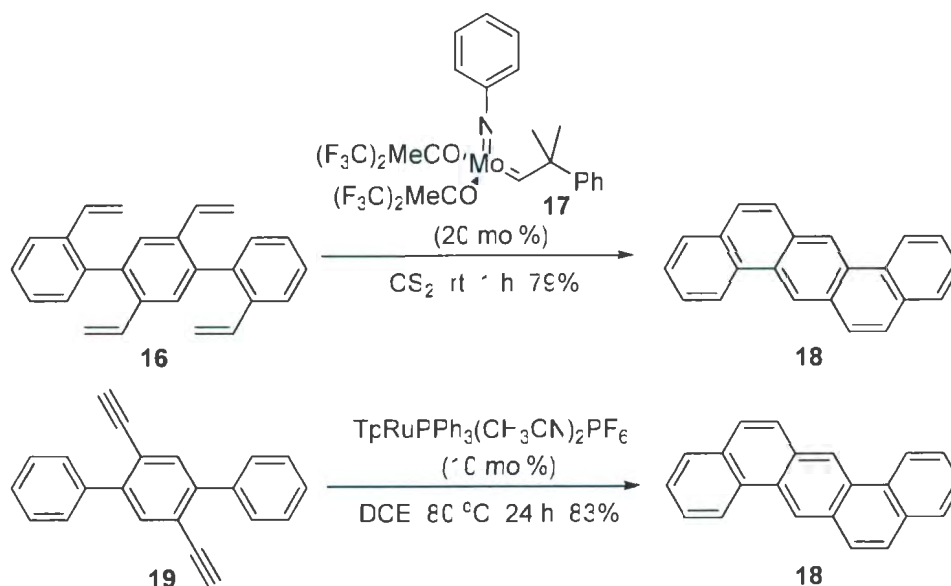
SCHEME 4.5 Synthesis of **22**
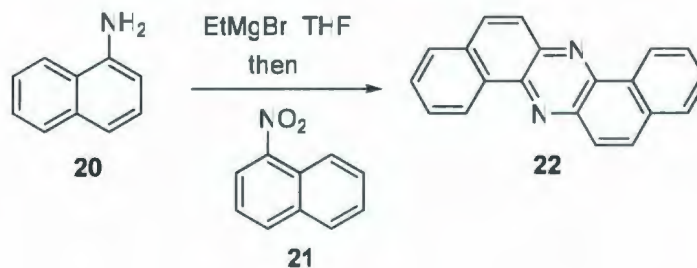
Previous work in the Bodwell group resulted in the discovery of a benzocoumarin-forming reaction (Scheme 4.6)[13] analogous to the conversion of diene **6** to xanthone **8** (Scheme 4.2). Electron deficient diene **25**, which can be prepared easily in multigram quantities from salicylaldehyde (**23**) and dimethyl glutaconate (**24**), reacts with enamines such as **26** and **7** to afford benzocoumarins **29** and **31**, respectively, albeit by slightly different mechanisms. It was therefore envisaged that this chemistry might be utilized for the synthesis of coumarin-based hetero[*n*]isophenacenes, which will be referred to as coum[*n*]isophenacenes due to the presence of a repeating coumarin unit. The value of *n* still represents the total number of rings to maintain homology to the parent [*n*]isophenacenes.

For the synthesis of coum[*n*]isophenacenes, an iterative strategy was envisioned (Scheme 4.7). The key feature of this strategy is to be able to either directly generate benzocoumarins with a salicyclaldehyde substructure, *i.e.* **32**, or, more likely, convert the products of the existing methodology into such systems. As such, each iteration would consist of three stages: (1) diene synthesis (salicylaldehyde reacting with dimethyl glutaconate), *e.g.* **32** to **33**, (2) benzocoumarin formation (IEDDA-driven

domino reaction), *e.g.* **33** to **34** and (3) regeneration of the salicylaldehyde subunit (functional group interconversion), *e.g.* **34** to **35**.

SCHEME 4.6 Synthesis of Benzocoumarins by IEDDA-Driven Domino Reactions
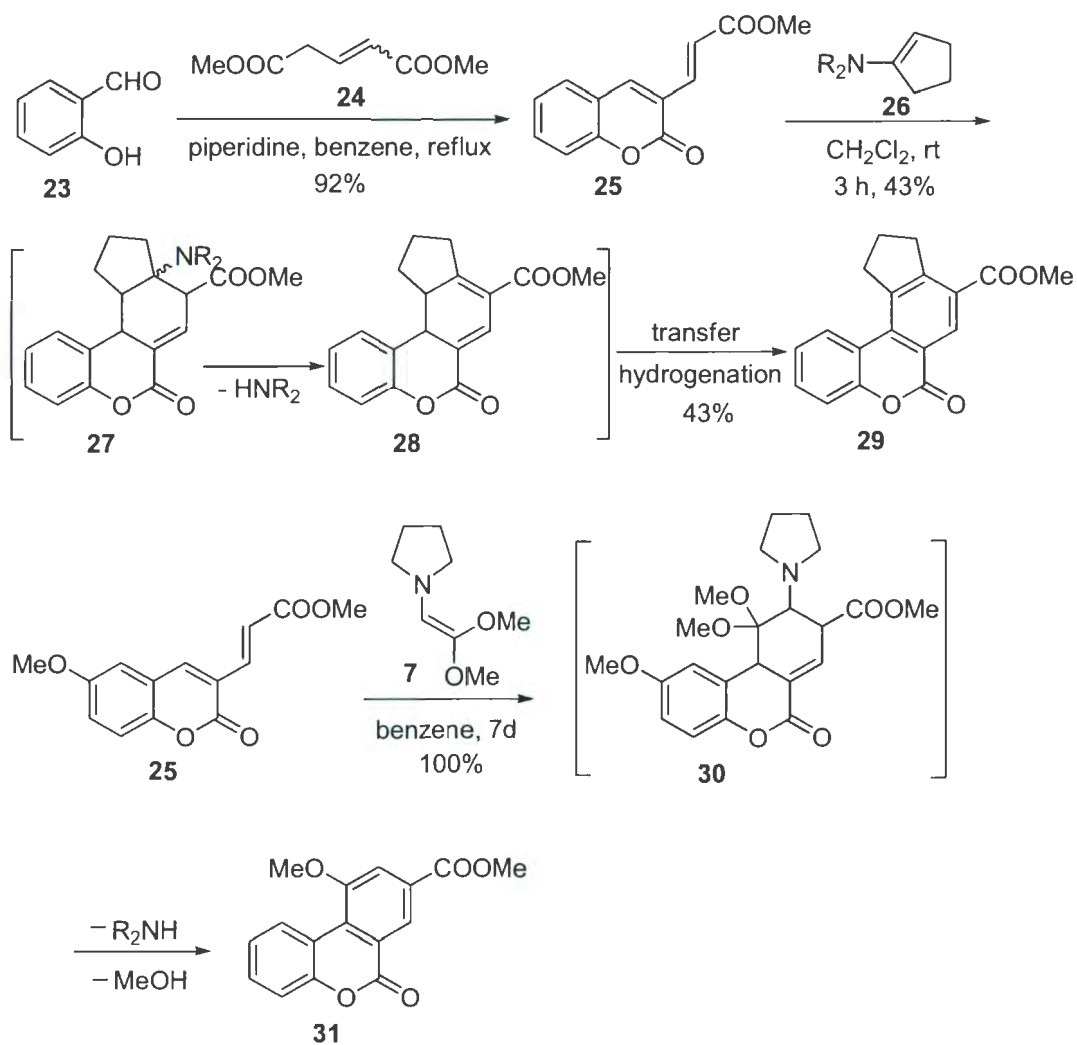
SCHEME 4.7 Proposed Iterative Strategy for the Synthesis of Coum[*n*]isophenacenes
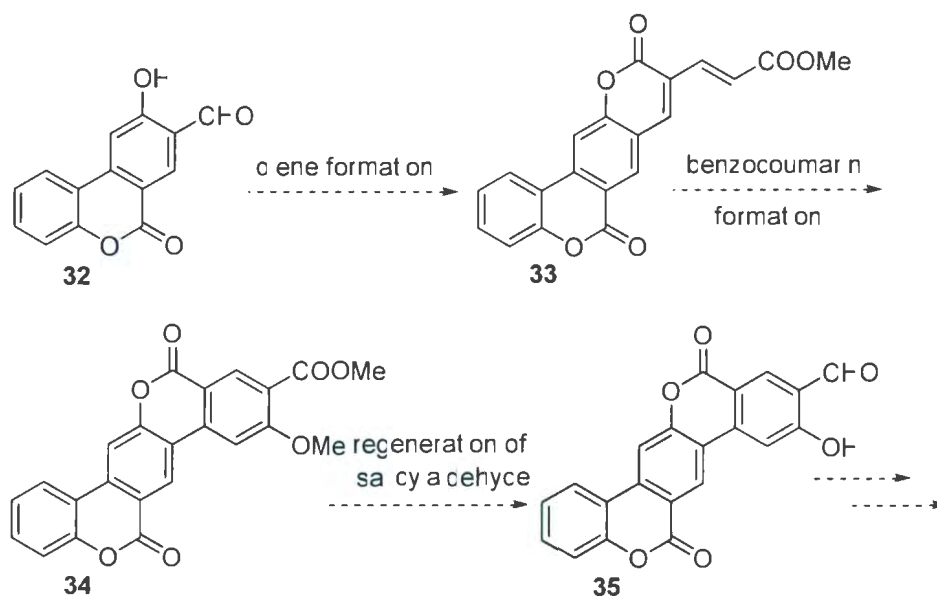
The initial target for this type of molecules would be coum[5]isophenacene **36** (Fig. 4.5). A long chain alkyl group was included in the target molecule for the purpose of maintaining solubility.
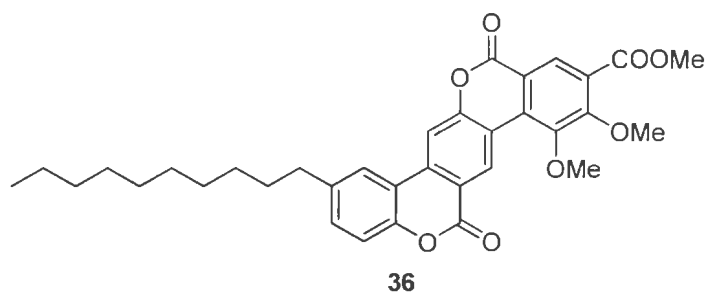
FIGURE 4.5. Coum[5]isophenacene **36**

4.2 Results and Discussion

The synthesis commenced with condensation of 5-bromosalicyladehyde (**37**) and dimethyl glutaconate (**24**), which afforded coumarin-fused electron deficient diene **38** in 87% yield (Scheme 4.8).[13] This diene was then reacted with tetramethoxyethene (**39**), which was available in the Bodwell laboratory.[14] The intention was to effect an IEDDA reaction followed by the loss of two equivalents of methanol from the initially formed adduct to afford benzocoumarin **40**. This compound bears an oxygen-based substituent adjacent to the ester, which offers the potential for the generation of a salicylaldehyde unit through selective demethylation of the methoxy group and reduction of the ester.

SCHEME 4.8 Synthesis of Coumarin-fused Diene **38**
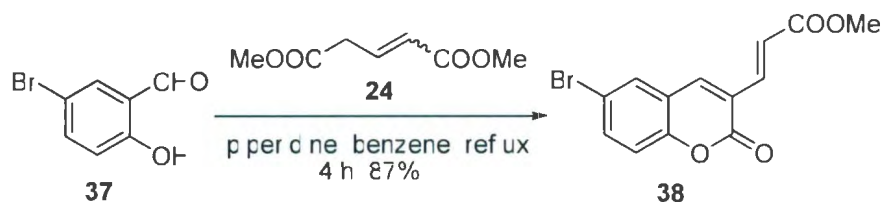
Not unexpectedly, no reaction was evident at room temperature or reflux in dichloromethane (Table 4.1, Entry 1). At reflux in acetonitrile, slow consumption of diene **38** was observed along with the development of a major new compound (^{1}H NMR analysis), but complete conversion was not observed after heating for 84 hours. However, the desired benzocoumarin **40** was obtained in 48% yield (Entry 2, Table 4.1). When the reaction was performed without solvent at 140 °C for 72 hours, benzocoumarin **40** was isolated in 70% yield (Entry 3, Table 4.1). For this reaction, 5.0 equivalents of

315

the dienophile were used. Although the yield was satisfactory, some efforts were made to optimize the reaction. The use of 2.5 equiv of the dienophile did not afford a homogeneous solution, even after heating at 140 °C for 96 hours. At this time, the reaction was still incomplete (approximately 75% conversion by ^{1}H NMR) and the yield was not determined (Entry 4, Table 4.1).

TABLE 4.1 IEDDA Driven Domino Reaction for the Synthesis of Benzocoumarin **28**
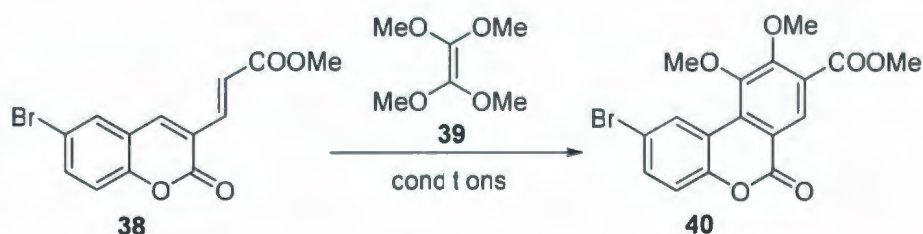
Entry	Dienophile (equiv)	Reaction conditions	Yield (%)^a
1	5.0	CH$_2$Cl$_2$, reflux, 84 h	0
2	5.0	CH$_3$CN, reflux, 84 h	48
3	5.0	neat, 140 °C, 72 h	70
4	2.5	neat, 140 °C, 96 h	n.d.
5	2.5	C$_2$H$_2$Cl$_4$, 140 °C, 44 h	74

^{a} isolated yield

It had been reported that 1,1,2,2-tetrachloroethane was a good solvent for the reaction of diene **6** with tetramethoxyethene (**39**),[7] but its use in the reaction of diene **38** with tetramethoxyethene (**39**) offered very little advantage over the solventless reaction

in terms of yield (74%). However, the number of equivalents of the dienophile could be reduced to 2.5 and the reaction time could be reduced to 44 hours.

The next task in the synthesis was to install the solubilizing group on the benzocoumarin moiety. Bromobenzocoumarin **40** was subjected to Sonogashira coupling with 1-decyne (**41**) in benzene with triethylamine as the base (Scheme 4.9). The reaction was very slow, giving only 21% of the desired alkyne **42** along with 57% recovery of **40** after 48 hours at reflux. The use of triethylamine as both the solvent and the base did not improve the yield significantly (30%). However, the employment of benzene as the solvent and DBU as the base proved to be beneficial. Complete consumption of the starting material was achieved after 4.5 hours at reflux and the isolated yield of **42** rose to 61%. Catalytic hydrogenation of **42** using 10% Pd/C then afforded decyl-substituted benzocoumarin **43** in 95% yield.

SCHEME 4.9 Synthesis of Triol **44**
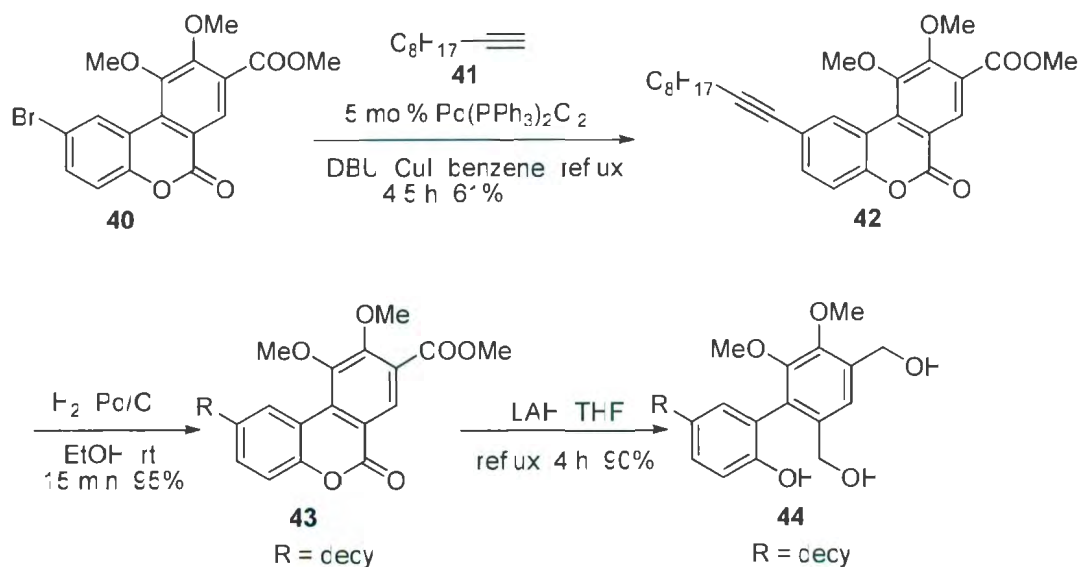
The next goal was to install formyl and hydroxy functional groups on C-8 and C-9 of the benzocoumarin structure, respectively. In this direction, ester **43** was reduced with LAH to afford triol **44** in 90% yield. Oxidation of this triol with a mild oxidant was expected to afford the desired aldehyde directly. The initially-formed dialdehyde **45** would be expected to form hemiacetal **46** and then undergo further oxidation to restore the benzocoumarin system.[13]

When **44** was subjected to reaction with Fetizon's reagent (Ag_2CO_3/Celite®),[15] no reaction was observed at room temperature or reflux in benzene, but the application of PCC afforded the desired aldehyde **47** in 50% yield when the reaction was performed on a 40 mg scale. However, when the reaction was performed on a larger scale (250 mg), more products were observed by tlc analysis and the yield of the desired aldehyde was only 10% (Scheme 4.10). In view of the small amounts of material that were available at this point, work on this project was discontinued.

Considering the large number of mild oxidants that are available, it is reasonable to assume that conditions will eventually be found for the efficient conversion of **44** to **47** on a multigram scale. Based on previous results from the Bodwell laboratory (*viz.* the conversion of **11** to **12** in Scheme 4.3), aldehyde **47** is expected to undergo highly selective demethylation to afford a formylhydroxy compound **48**,[16] which is the starting point for a second iteration.

SCHEME 4.10 Synthesis of Aldehyde **47**
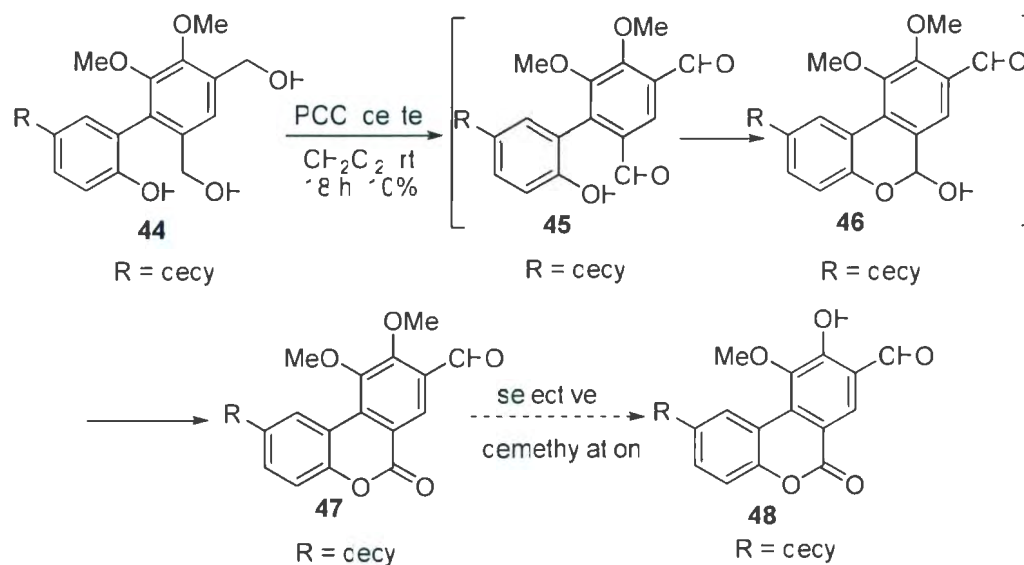
4.3 Conclusion

An iterative strategy for the synthesis of a novel class of polycyclic heteroaromatic compounds (coum[*n*]isophenacenes) has been proposed and preliminary synthetic work has been conducted. Although a full iteration was not completed, some useful groundwork has been laid for future investigations.

4.4 Experimental

4.4.1 General Methods

All reactions were carried out using oven-dried glassware with inert gas protection, unless otherwise mentioned. THF and benzene were dried and distilled over sodium/benzophenone. Dichloromethane was dried and distilled over CaH_2. All other chemicals, including solvents, were used as received without further purification. Thin layer chromatography (tlc) was performed on MN PolyGram precoated silica gel plates using 254 nm UV visualization. Flash chromatography was performed on silica gel columns. Melting points were recorded on Fisher-Johns apparatus and are uncorrected. All proton and carbon assignments are based on 2D NMR experiments (COSY, HMQC and HMBC). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE spectrometer at 500.133 MHz and 125.770 MHz, respectively. Peaks reported are relative to internal standards: TMS (δ = 0.00) for ^{1}H and $CDCl_3$ (δ = 77.23) for ^{13}C spectra. Reported multiplicities are apparent. Infrared spectra were obtained on Bruker Tensor 27 instrument using neat samples. Low-resolution mass spectra were obtained using using Agilent 1100 series LC/MS chromatographic system and high-resolution mass spectra were obtained using Waters GCT Permier Micromass mass spectrometer.using neat samples.

4.4.2 Synthesis and Characterization

Methyl 2-bromo-9,10-dimethoxy-6-oxo-6*H*-benzo[*c*]chromen-8-carboxylate (40)
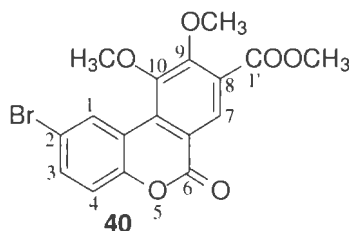
A mixture of **38** (1.28 g, 4.16 mmol), **39** (1.55 g, 10.5 mmol) and 1,1,2,2-tetrachloroethane (1 mL) was heated at 135-140 °C for 44 h. The pale yellow suspension turned into a clear, yellow solution as the heating progressed. The reaction mixture was cooled to room temperature and diluted with acetonitrile. The resulting pale yellow precipitate was filtered under suction, washed with acetonitrile and air-dried to afford **40** as an off-white solid (1.21 g, 74%). mp = 229-231 °C (chloroform/hexane); δ_H(CDCl$_3$) = 9.19 (d, J = 2.6 Hz, 1H, H-1), 8.66 (s, 1H, H-7), 7.63 (dd, J = 8.8, 2.2 Hz, 1H, H-3), 7.25 (d, J = 9.0 Hz, 1H, H-4), 4.09 (s, 3H), 4.01 (s, 3H), 3.97 (s, 3H) ppm; δ_C(CDCl$_3$) = 164.7 (C-1′), 159.7 (C-6), 159.2, 151.7, 150.6, 134.2 (C-7), 130.8, 130.7 (C-1), 129.6 (C-3), 127.3, 119.5 (C-4), 118.7, 117.9, 117.7, 62.2, 60.6, 52.9 ppm; HRMS [M$^+$] calcd for C$_{17}$H$_{13}$O$_6$ Br 391.9889, found 391.9895.

Methyl 2-(dec-1-ynyl)-9,10-dimethoxy-6-oxo-6*H*-benzo[*c*]chromene-8-carboxylate (42)
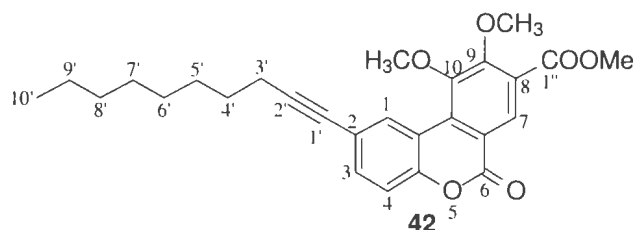
To a mixture of CuI (0.064 g, 20 mol%) and Pd(PPh$_3$)$_2$Cl$_2$ (0.12 g, 10 mol%) was added a clear, pale yellow solution of **40** (0.655 g, 1.67 mmol) in benzene (30 mL) followed by DBU (1.0 mL, 6.7 mmol) and 1-decyne (**41**) (1.21 mL, 6.7 mmol) sequentially. The resulting dark brown solution was then heated at reflux for 13 h. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (30 mL) and filtered under suction through a pad of Celite®. The residue was washed with dichloromethane (10 mL). The filtrate was sequentially washed with saturated NH$_4$Cl (20 mL) solution, brine (10 mL) and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (10% ethyl acetate/hexanes) to afford **42** as a pale yellow oil (0.46 g, 61%). δ_H(CDCl$_3$) = 8.96 (d, *J* = 2.0 Hz, 1H, H-1), 8.65 (s, 1H, H-7), 7.52 (dd, *J* = 9.1, 1.9 Hz, 1H, H-3), 7.27 (d, *J* = 9.1 Hz, 1H, H-4), 4.09 (s, 3H), 4.01 (s, 3H), 3.97 (s, 3H) 2.44 (t, *J* = 6.9 Hz, 2H, H-3′), 1.64 (p, *J* = 7.2 Hz, 2H, H-4′), 1.48 (p, J = 6.6 Hz, 2H, H-5′), 1.37-1.30 (m, 8H), 0.89 (t, *J* = 6.7 Hz, 3H, H-10′) ppm; δ_C(CDCl$_3$) = 164.3 (C-1″), 160.2 (C-6), 159.5,

151.1, 149.6, 139.9, 132.0 (C-1), 131.3 (C-3), 129.7 (C-7), 127.2, 122.5 (C-4), 121.1,

118.6, 117.7, 101.9 (C-2′), 81.4 (C-1′), 61.9, 60.1, 52.5, 30.1 (C-3′), 29.7, 29.6, 29.4,

22.0, 14.5 (C-10′) (two carbon signals fewer than expected, presumably due to accidental

degeneracy) ppm; HRMS [M$^+$] calcd for $C_{27}H_{30}O_6$ 450.2042, found 450.2046.

Methyl 2-decyl-9,10-dimethoxy-6-oxo-6H-benzo[c]chromene-8-carboxylate (43)
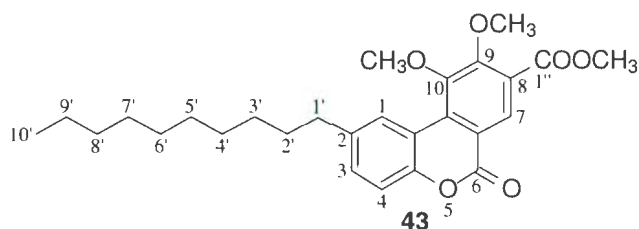
To a clear, yellow solution of alkyne **41** (0.41 g, 0.91 mmol) in ethanol (30 mL) was

added Pd/C (0.041 g, 10% by weight) and the reaction mixture was stirred under

hydrogen atmosphere at room temperature for 14 h. The reaction mixture was filtered

through a pad of Celite® and washed with ethanol. The solvent was removed from the

filtrate under reduced pressure to afford **43** as a colorless gum (0.39 g, 95%). δ_H(CDCl$_3$)

= 8.74 (d, J = 2.1 Hz, 1H, H-1), 8.68 (s, 1H, H-7), 7.39 (dd, J = 9.0, 2.1 Hz, 1H, H-3),

7.25 (d, J = 9.0 Hz, 1H, H-4), 4.07 (s, 3H), 3.97 (s, 3H), 3.96 (s, 3H) 2.72 (t, J = 6.9 Hz,

2H, H-1′), 1.67-1.64 (m, 2H, H-2′), 1.41 (br m, 2H, H-3′), 1.31-1.23 (m, 12H), 0.89 (t, J

= 6.7 Hz, 3H, H-10′) ppm; δ_C(CDCl$_3$) = 164.2 (C-1″), 160.2, 159.7, 151.2, 149.9, 140.0,

131.8, 131.4, 129.8 (C-7), 128.1, 127.2, 118.7, 118.6, 117.7, 62.1, 60.2, 52.7, 36.7 (C-1′),

31.4 (C-2′), 29.8, 29.71, 29.68, 29.6, 22.3, 14.7 (C-10′) (two carbon signals fewer than expected, presumably due to accidental degeneracy) ppm; HRMS [M$^+$] calcd for C$_{27}$H$_{34}$O$_6$ 454.2355, found 454.2352.
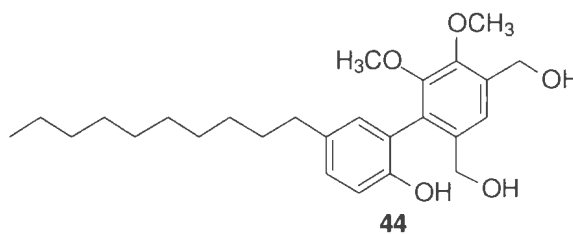
5-Decyl-4',6'-bis(hydroxymethyl)-2',3'-dimethoxybiphenyl-2-ol (44)

44

To a 0 °C supension of LAH (0.053 g, 1.4 mmol) in THF (2 mL) was added a solution of ester **43** (0.32 g, 0.70 mmol) in THF (5 mL) over a period of 5 min. The resulting mixture was heated at reflux for 16 h. The reaction mixture was cooled to room temperature and then cooled in an ice bath. Ice-cold water (1 mL) was added to the reaction mixture dropwise followed by the addition of 15% NaOH (1 mL) solution followed by 1M HCl (10 mL). The reaction mixture was saturated by adding NaCl and then extracted with ethyl acetate (2 × 25 mL). Combined organic layers were washed with brine (15 mL), dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure to afford **44** as brown oil (0.27 g, 90%). Major peaks in the ^{1}H and ^{13}C NMR of the crude product are listed below. (This compound was used as such for the next step). δ$_H$(CDCl$_3$) = 7.11-7.09 (m, 2H), 6.93-6.91 (m, 2H), 4.72 (s, 2H), 4.34 (s, 2H),

3.94 (s, 3H) 3.57 (s, 3H), 3.39 (br s, 2H), 2.54 (br m, 2H), 1.58 (br m, 2H), 1.29-1.24 (m, 14H), 0.88 (br m, 3H) ppm; δ_C(CDCl$_3$) = 156.2, 151.0, 150.2, 135.2, 131.9, 130.8, 130.0, 125.4, 125.3, 124.6, 123.4, 116.4, 63.6, 61.2, 60.9, 35.3, 31.9, 29.7, 29.71, 29.68, 29.5, 22.9, 14.4 (three carbon signals fewer than expected) ppm; [M$^+$] calcd for $C_{27}H_{38}O_5$ 430.2719, found 430.2711.

2-Decyl-9,10-dimethoxy-6-oxo-6*H*-benzo[*c*]chromene-8-carbaldehyde (47)

47
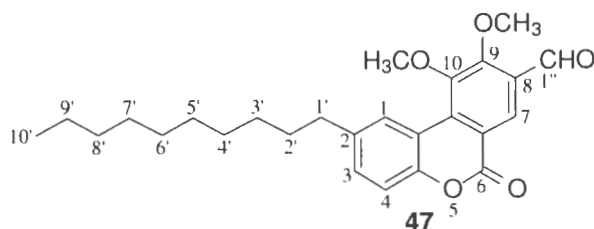
To a clear, yellow solution of PCC (1.1 g, 2.9 mmol) in dichloromethane (30 mL) was added a clear, brown solution of triol **44** (0.25 g, 0.58 mmol) in dichloromethane (6 mL) followed by the addition of Celite® (1.0 g). The reaction mixture was stirred at room temperature for 20 h and then filtered under suction. The solvent was removed under reduced pressure and subjected to flash chromatography (20% ethyl acetate/hexanes) to afford **47** as a white solid (0.024 g, 10%). mp = 182-183 °C (ethyl acetate/hexanes).

δ_H(CDCl$_3$) = 10.48 (s, 1H, H-1''), 8.76 (d, J = 2.1 Hz, 1H, H-1), 8.37 (s, 1H, H-7), 7.35 (dd, J = 8.5, 2.2 Hz, 1H, H-3), 7.24 (d, J = 8.5 Hz, 1H, H-4), 4.19 (s, 3H), 3.99 (s, 3H), 2.73 (t, J = 7.1 Hz, 2H, H-1'), 1.72-1.70 (m, 2H, H-2'), 1.11-1.28 (m, 14H), 0.87 (t, J =

7.0 Hz, 3H, H-10′) ppm; $\delta_C(CDCl_3)$ = 188.2 (C-1′′), 160.9 (C-6), 160.3, 150.9, 150.0, 139.8, 134.3, 132.2 (C-1), 129.8, 127.9 (C-7), 127.5 (C-3), 118.4, 117.7 (C-4), 116.6, 62.6, 60.4, 35.9 (C-1′), 32.1 (C-2′), 31.8, 29.8, 29.7, 29.5, 29.4, 22.9, 14.3 (C-10′) (one carbon signal fewer than expected) ppm; HRMS [M⁺] calcd for $C_{26}H_{32}O_5$ 424.2250, found 424.2251.

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4.6 Appendix

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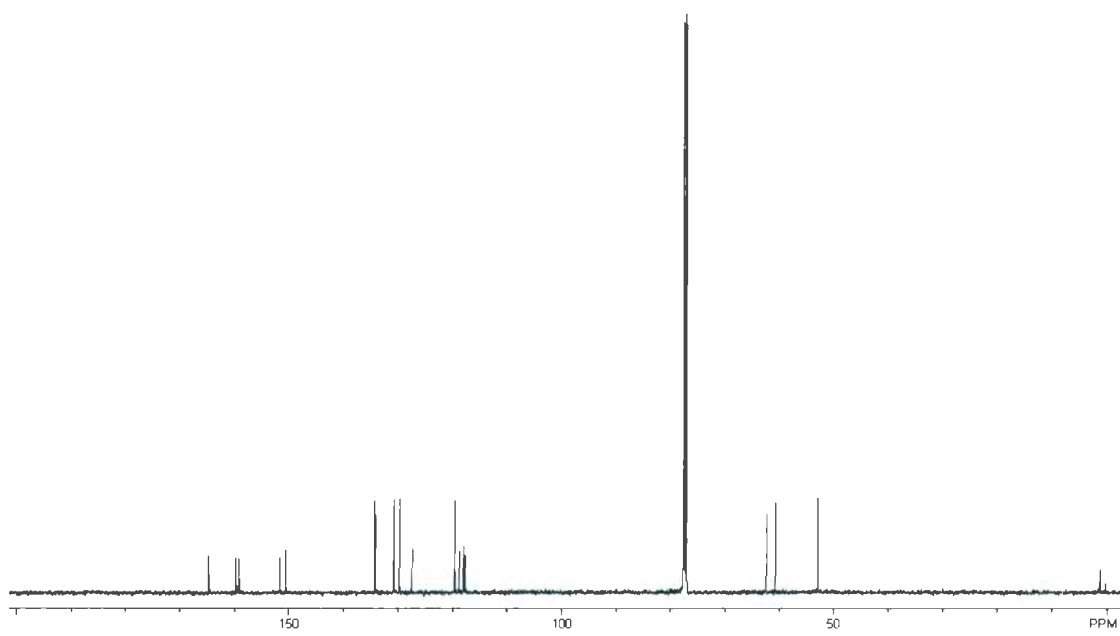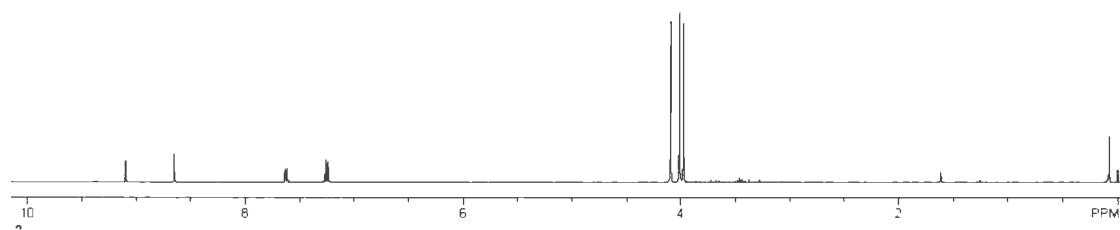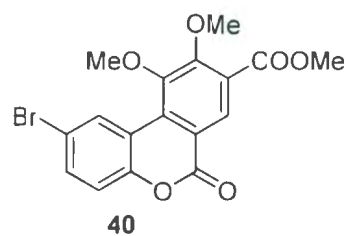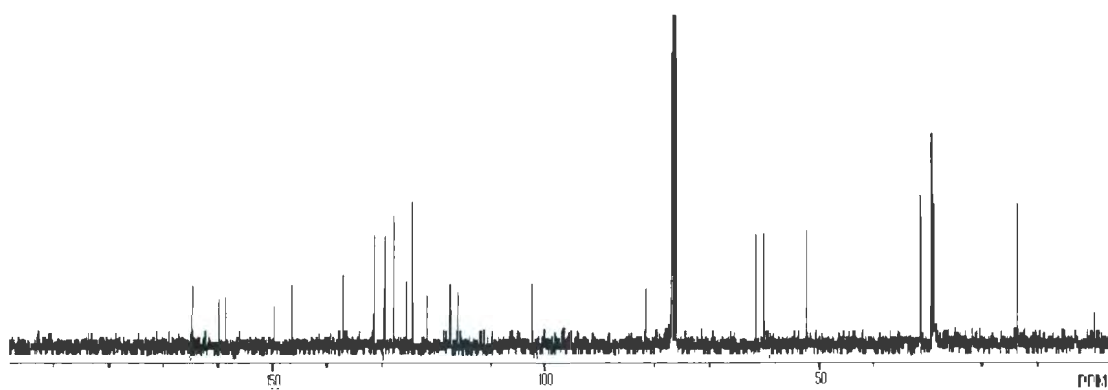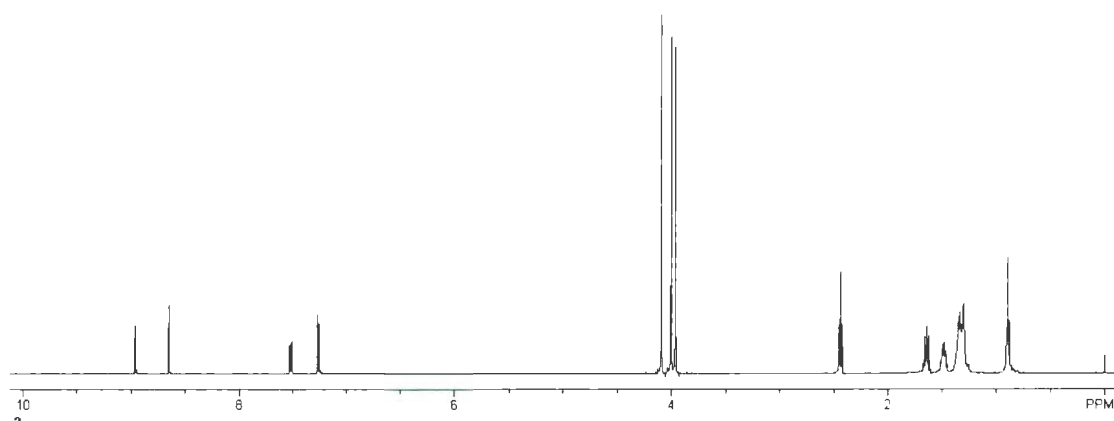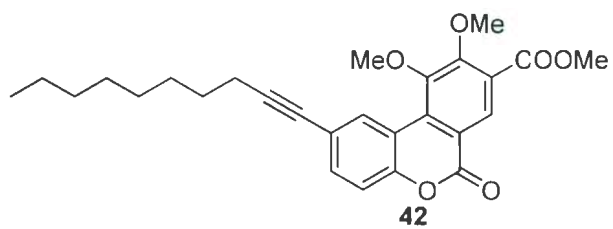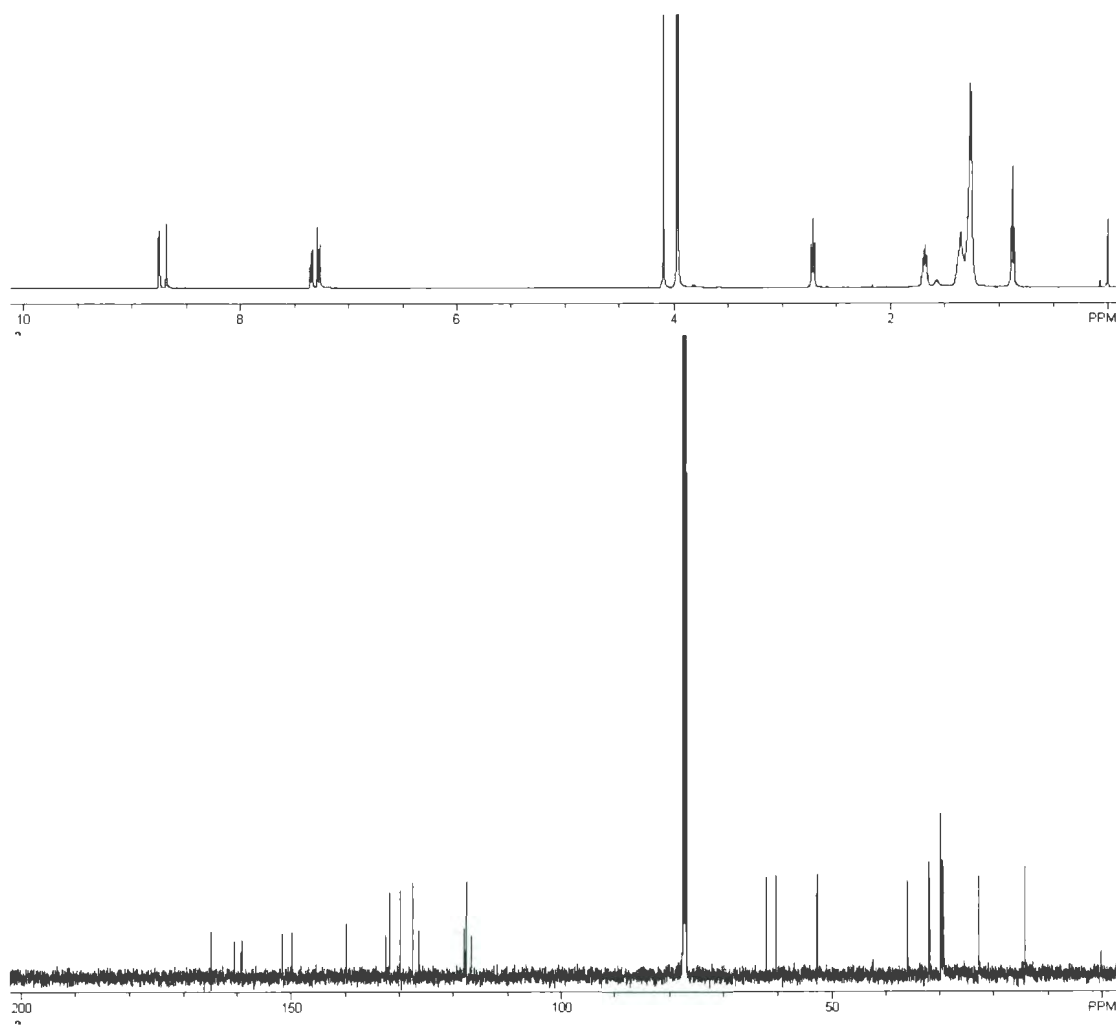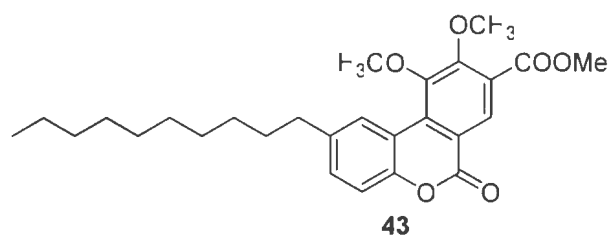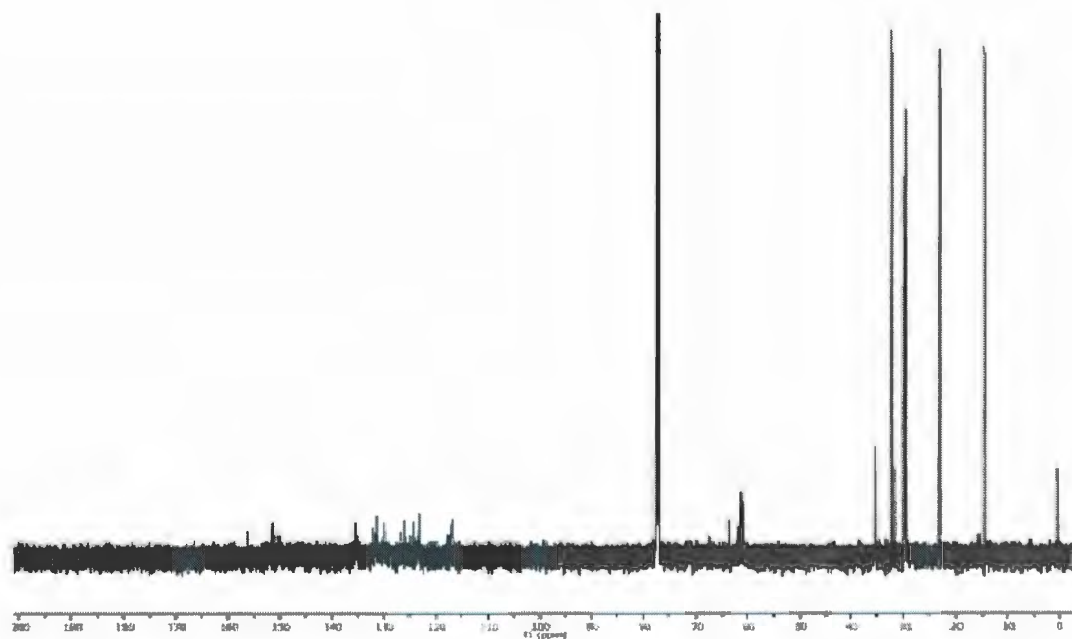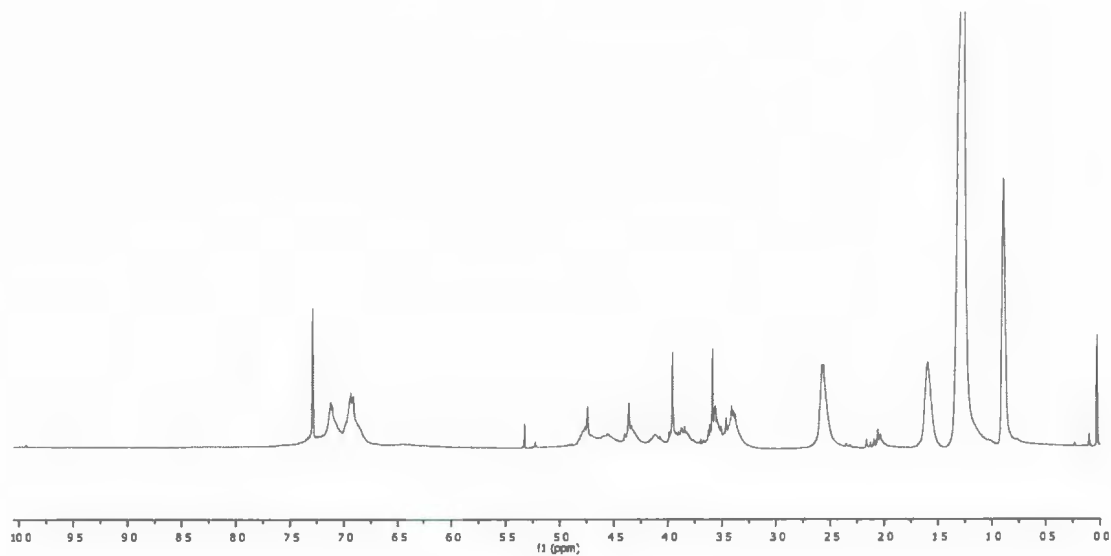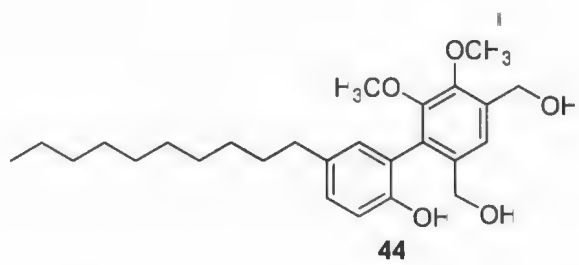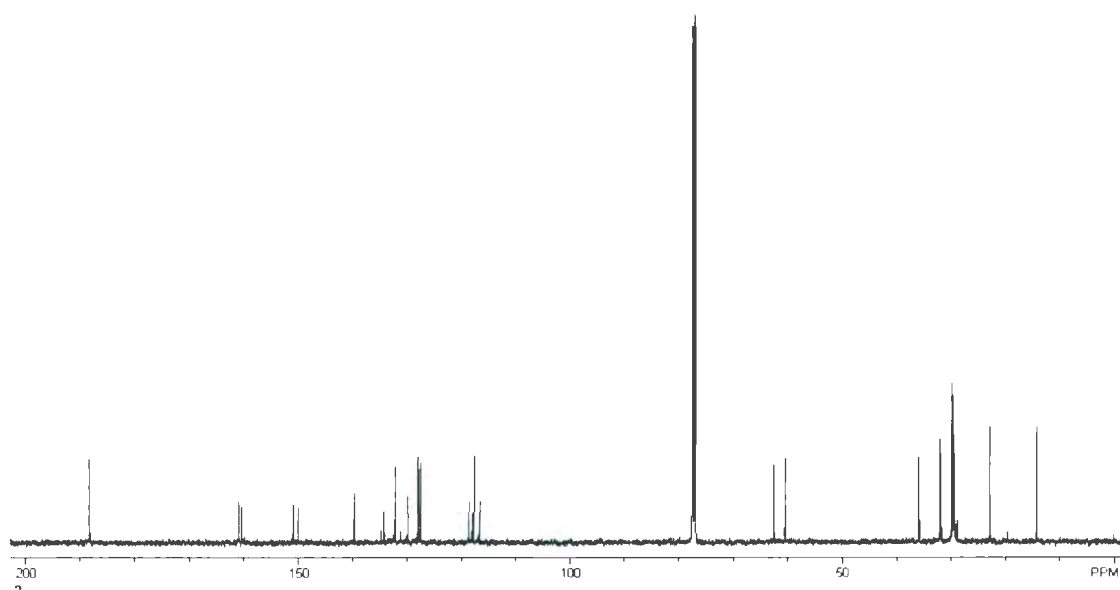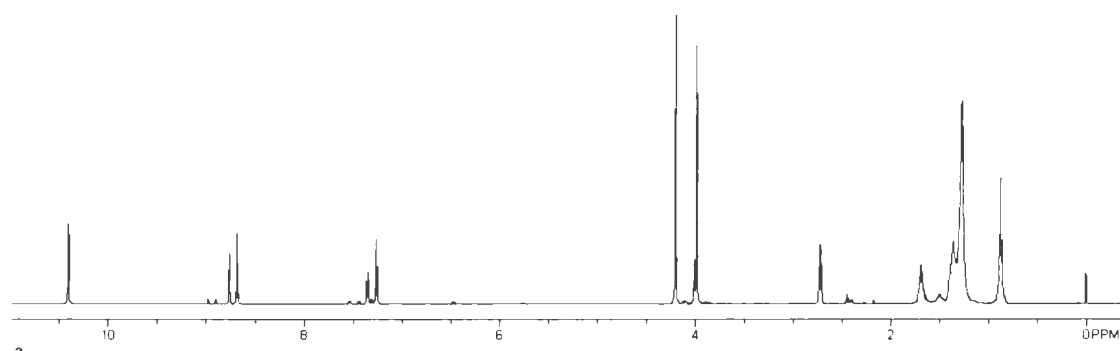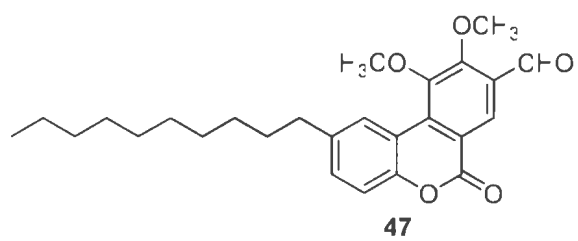
Chapter 5. Toward the Synthesis of a Naphtho-fused

[7]Helicene

5.1 Introduction

According to IUPAC, "helicenes are *ortho*-fused polycyclic aromatic compounds in which all rings (minimum five) are angularly arranged so as to give helically shaped molecules, which are thus chiral."[1] The helical structure of these molecules is a result of severe steric repulsions between nonbonded atoms when the molecule adopts the planar conformation. Due to the presence of an inherently chiral chromophore and the possibility of intramolecular through-space interactions between the overlapping aromatic rings, helicenes have attracted considerable attention in recent years[2] and interesting optical and electronic properties of helicenes have been revealed.[3]
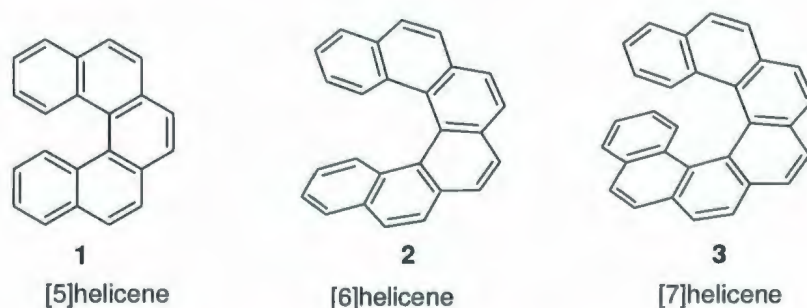
FIGURE 5.1 [5]Helicene **1**, [6]helicene **2**, and [7]helicene **3**

Helicenes **1**, **2** and **3** having 5, 6 and 7 *ortho*-fused benzene rings, respectively, are shown in Fig. 5.1. While IUPAC nomenclature can be used for systematically

naming such molecules, a simpler system is usually followed for their nomenclature. According to this system, the number of rings present in the compound is indicated by a number in square brackets followed by the word 'helicene'. Thus, compounds 1, 2 and 3 are named as [5]helicene, [6]helicene and [7]helicene, respectively.

Helicenes having aromatic rings other than benzene (*e.g.* thiophene) have also been known for a long time.[4] A variety of helicenes, including heterohelicenes[5] and carbohelicenes as large as [14]helicene,[6] have been prepared. A classical method for the preparation of helicenes is photocyclization of stilbene derivatives into the corresponding phenanthrene derivatives in the presence of an oxidizing agent.[7] However, this method suffers from serious drawbacks such as regioselectivity of the cyclization[8] and photodimerization[9] of the stilbene derivatives to afford cyclobutane-derivatived byproducts (Scheme 5.1). Another problem with the photochemical cyclization is that the scale is limited. Therefore, it is unsuitable for the preparation of larger amounts of helicenes, which are required for the exploration of their chemical and physical properties as well the exploitation of these properties, *e.g.* in optoelectronic devices.

A major breakthrough in this field was reported by Katz, who utilized a Diels-Alder-based approach in the synthesis of various helicene quinones.[10] This method enabled the synthesis of sufficient quantities of helicenes for the study of their properties. Other nonphotochemical methods have been developed for the syntheses of helicenes and these include carbenoid insertion,[11] [2+2+2] cycloisomerization,[12] tandem radical cyclization,[13] ring closing metathesis,[14] double direct arylation[15] and, more recently,

SCHEME 5.1 Drawbacks in the Photocyclization of Stilbene Derivatives
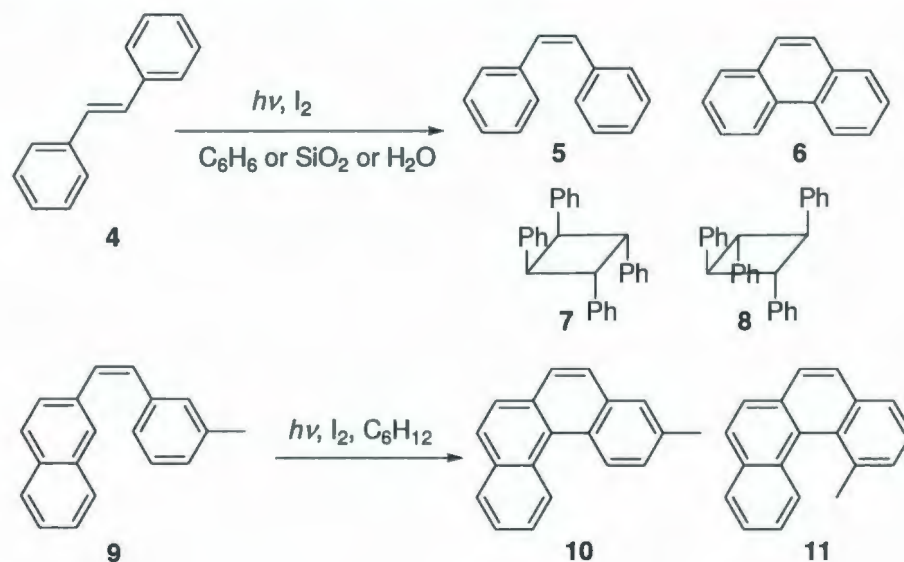
Friedel-Crafts-type cyclization of 1,1-difluoro-1-alkenes.[16] Among these methods, the most general and atom-economical method appears to be the one developed by Starý and coworkers. In this approach, a nickel- or cobalt-catalyzed [2+2+2] cycloisomerization of triynes is used as the key skeleton-building reaction. For example, triynes **12** or **13** can be cycloisomerized to the corresponding helicene precursors, which are then converted into helicene **1** by dehydrogenation or elimination-dehydrogenation (Scheme 5.2). A variety of substrates has been employed in this reaction and thus various helicenes, including azahelicenes and other helicene-like molecules, have been constructed by the Starý group.[12]

A common feature of all of the helicenes reported so far is that the helical aromatic backbone is as wide as a single benzene ring or other heteroaromatic unit.

Helicenes having wider aromatic backbones are unprecedented. Such helicenes are obtained upon benzannulation of the outer edge of a parent helicene (Fig. 5.2). For

SCHEME 5.2 [2+2+2] Cycloisomerization for the Synthesis of Helical Backbone
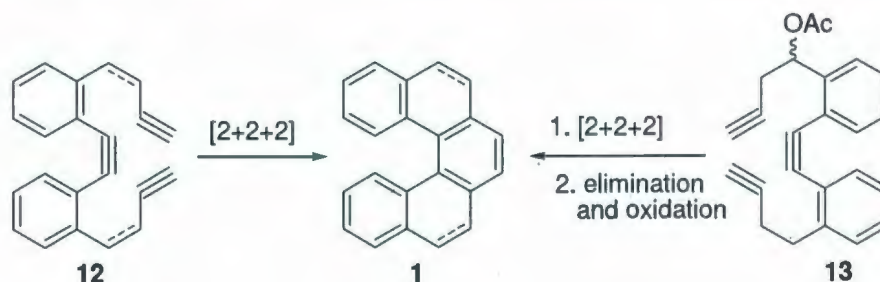
example, benzannulation of the outer edge of [5]helicene (**1**) affords helical arene **14**. A second benzannulation process gives a wider helical system **15**. The synthesis of such targets, or even partially benzannulated helicenes, is a daunting task with the available synthetic methodology.
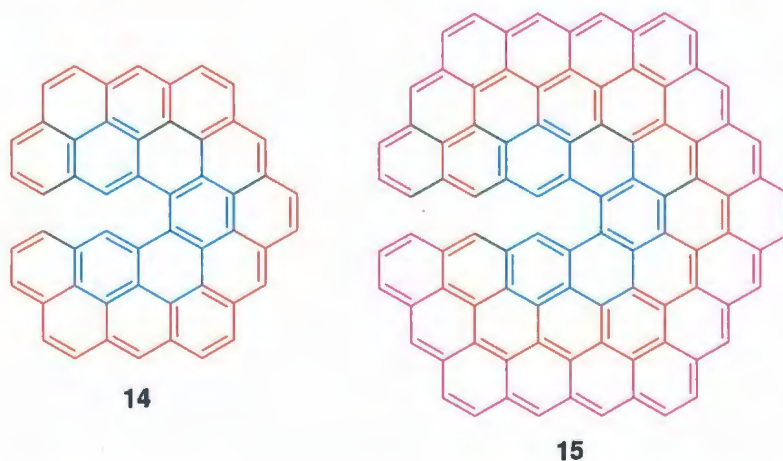
FIGURE 5.2 Helicenes With Wider Aromatic Backbones

The first step toward achieving such a goal would be the incorporation of wider aromatic pieces (such as naphthalene, phenanthrene and or pyrene) at either or both of the termini of a helicene. In the course of efforts directed toward the synthesis of a coumarin-fused 2-azadiene having a pyrene unit at one end, a functionalized pyrene derivative **16** (Fig. 5.3) was prepared,[17] which has the functionality that might be exploited to prepare helicene precursors using Starý's methodology. Therefore, a target which can be viewed as a naphtho-fused [7]helicene **17** was designed for preliminary work in this area (Fig. 5.3).

FIGURE 5.3 A Functionalized Pyrene Derivative **16** and Naphtho-fused [7]Helicene **17**

5.2 Retrosynthetic Analysis

5.2.1 Retrosynthetic Plan 1
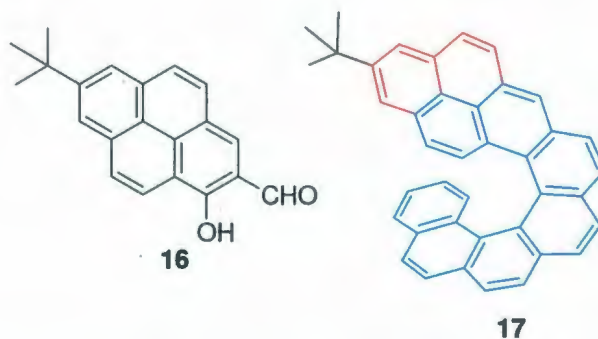
Based on the [2+2+2] cycloisomerization strategy for building the central three rings of the naphtho-fused [7]helicene **17**, the first retrosynthetic cut simplified the target to a triyne **18**, which contains pyrene and naphthalene pieces connected through an acetylenic linker. This triyne **18** could be the product of a Sonogashira reaction between diyne **19** and iodide **20** (Scheme 5.3). Diyne **19** is analogous to one previously reported

in which the same side chain is attached to a benzene ring.[18] Therefore, it was expected that the alkynic side chain at C-2 of the pyrene unit could be installed in a similar fashion *i.e.* from bromide **21** and a propargyl bromide-derived organometallic reagent. Bromide **21** can be traced back to the pyrene derivative **22** by way of a Sonogashira reaction. The other key intermediate required for this synthesis was iodide **20**, which has been synthesized previously in the Starý group.[18]

SCHEME 5.3 Retrosynthetic Plan 1

X = halide or pseudo halide
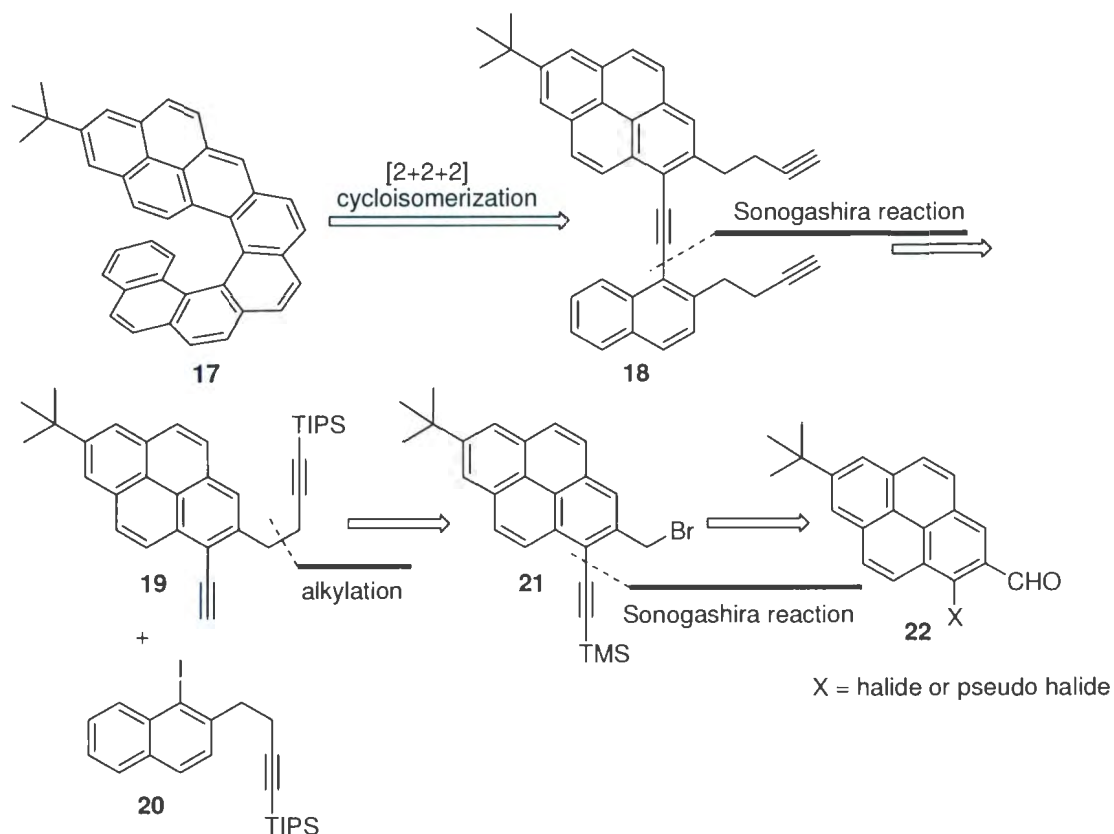
5.2.2 Retrosynthetic Plan 2

An alternative retrosynthetic plan was also prepared for this synthesis (Scheme 5.4). According to this plan, acetoxytriyne **23** was envisioned as a precursor to the helicene **17**. In the forward sense, cycloisomerization of the acetoxytriyne **23** followed by elimination and dehydrogenation would afford the helicene **17**. Intermediate **23** could be simplified in a retrosynthetic sense to an aldehyde **24**, which would be expected to undergo 1,2-addition with an appropriate organopropargyl reagent. Aldehyde **24**, which has two alkyne units, was envisioned to be the product of a Sonogashira reaction between a functionalized pyrene derivative **22** and a naphthalene-based diyne **25**, the synthesis of

SCHEME 5.4 Retrosynthetic Plan 2
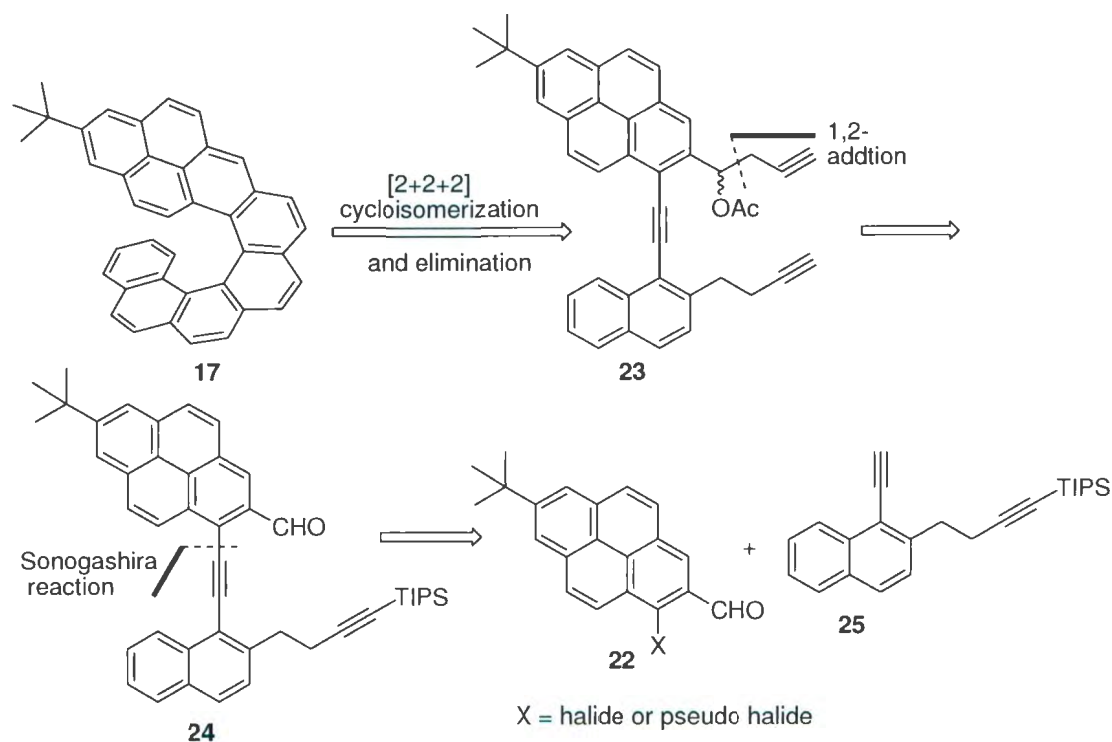
which was accomplished previously by the Starý group.[18]

5.3 Results and Discussion

5.3.1 Synthesis of 7-*t*-butyl-2-formyl-1-hydroxypyrene (29)

The first objective in the synthesis was the preparation of pyrene derivative **22**, which has an aldehyde functionality at C-2 and a halide or a pseudo-halide at C-1 of pyrene. For the purpose of maintaining solubility, the design included a 7-*t*-butyl group on the pyrene unit.

With the above-mentioned requirements in mind, 1-acetoxypyrene (**26**) was prepared from pyrene in two steps following a published method.[19] Subjection of **26** to Friedel-Crafts alkylation using *t*-BuCl/AlCl₃ afforded two major products: 7-*t*-butyl-1-acetoxypyrene (**27**) and 7-*t*-butyl-1-hydroxypyrene (**28**) in 49% and 35% yields, respectively. A slightly lower yield of **27** was obtained (42%) when the reaction was performed on a multigram scale (3.5 g), while the yield for **28** remained the same (35%). Hydrolysis of the ester functionality in **27** presumably occurred during aqueous workup to afford **28**. As expected, purified ester **27** was hydrolyzed easily under mild conditions to give **28** in almost quantitative yield. (Scheme 5.5).

Attempts to introduce an aldehyde functionality at the 2-position of 7-*t*-butyl pyrene-1-ol (**28**) by using Skattebøl[20] or modified Gattermann[21] formylation conditions were unsuccessful (Scheme 5.6). Therefore, a longer, but more reliable, route involving Directed *ortho* Metallation (DoM) chemistry[22] was chosen to synthesize the desired formylhydroxypyrene derivative **29**. 7-*t*-Butylpyrene-1-ol (**28**) was protected as a

carbamate **30** upon reaction with *N,N*-dimethylcarbamoyl chloride in the presence of triethylamine and a catalytic amount of DMAP to afford **30** in quantitative yield. In the absence of DMAP, no reaction was evident even after heating at reflux in CHCl₃ for 3 hours.

SCHEME 5.5 Synthesis of **28**
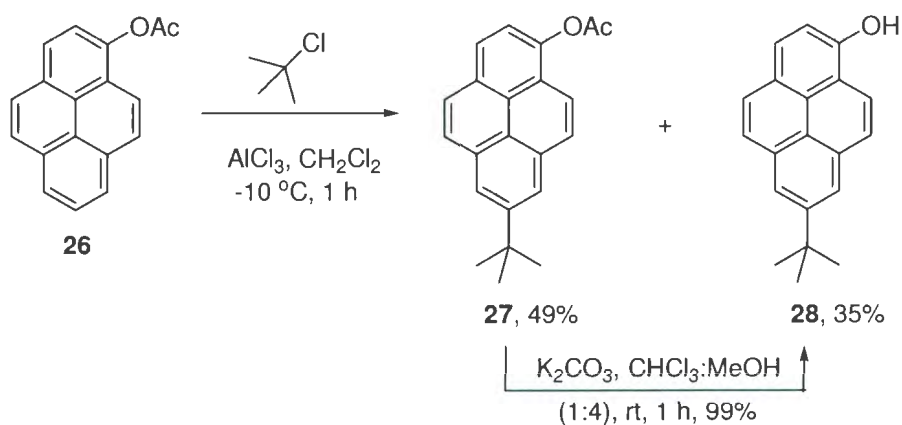
SCHEME 5.6 Attempted Formylation of **28**

(a) MgCl₂, Et₃N, (HCHO)ₓ, CH₃CN, reflux
(b) Zn(CN)₂, CHCl₃, HCl₍g₎
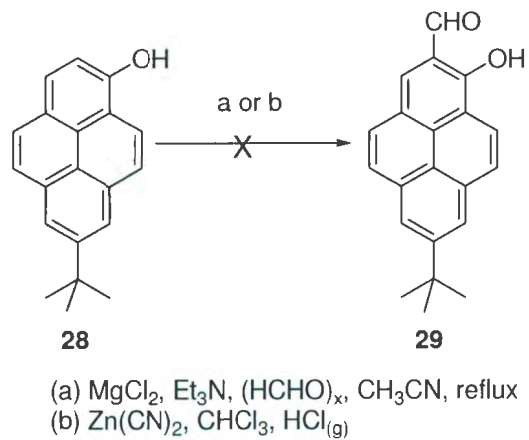
Carbamate **30** was reacted under typical DoM reaction conditions (*n*-BuLi, TMEDA, −78 °C, followed by the addition of DMF), but the desired product was not formed. Instead, the major product isolated from this reaction was **31** (55%), the product of 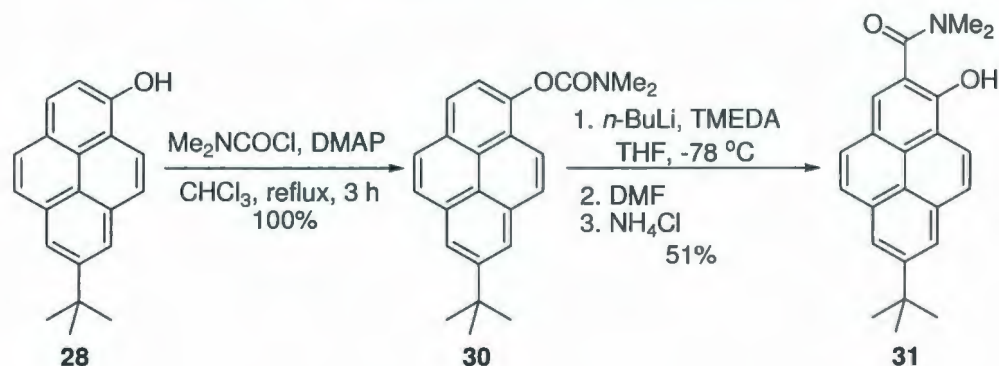an anionic *ortho*-Fries rearrangement (Scheme 5.7). 7-*t*-Butyl pyrene-1-ol (**28**) was isolated as a minor product (4%) from this reaction. This prompted the employment of other directing groups.

SCHEME 5.7 Anionic *ortho*-Fries Rearrangement of **30**

The *O*-MOM group has been reported to be a reasonable directing group for DoM chemistry on pyrene substrates.[19b] Therefore, *O*-MOM derivative **32** of 7-*t*-butyl pyrene-1-ol (**28**) was prepared. Initially, the reaction of **28** with methoxymethyl chloride (MOMCl) in the presence of an organic base, triethylamine was studied. However, this reaction was very slow. The reaction mixture had to be heated at reflux for 48 hours and only 74% of the alkylated product **32** was obtained. The use of a strong base, sodium hydride, not only accelerated the rate of reaction (1 hour at room temperature) but also

SCHEME 5.8 Synthesis of **33** Using *O*-MOM as a Directing Group
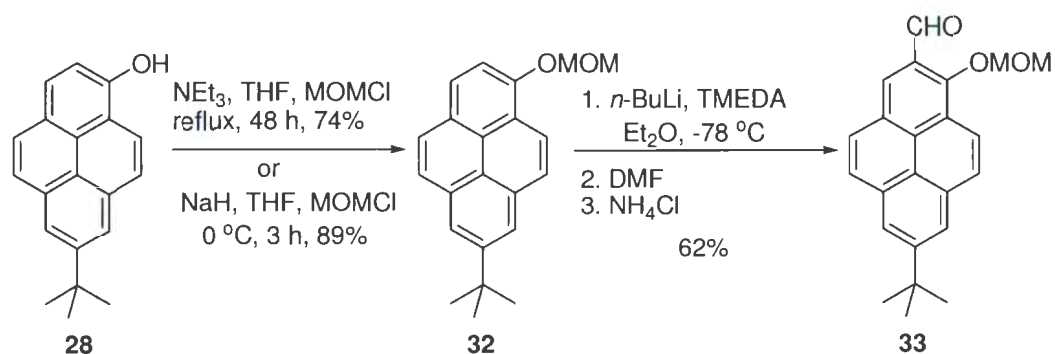
improved the yield to 89% (Scheme 5.8).

Following a literature procedure performed on a similar substrate,[15b] the D*o*M reaction was carried out in dry ether using *n*-BuLi and TMEDA followed by the addition of DMF to afford aldehyde **33** in 62% yield (Scheme 5.8). When diethyl ether was replaced by THF, a satisfactory yield (70%) of the desired product was obtained. The use of a different electrophile, *N*-methylformanilide afforded essentially the same yield (70%). Finally, the removal of the directing group was achieved in quantitaive yield

SCHEME 5.9 Synthesis of **29**

345
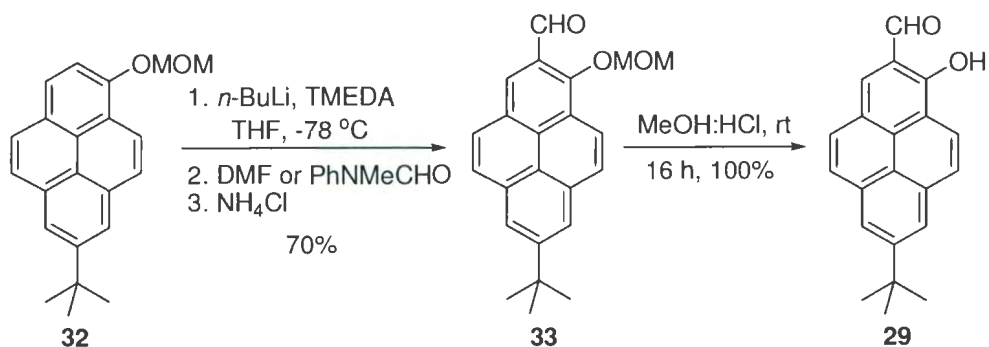
upon treatment of **33** with 2:1 MeOH: conc. HCl (Scheme 5.9). This afforded 7-*t*-butyl-2-formyl-1-hydroxypyrene (**29**) and completed the first stage of the synthesis.

5.3.2 Approach 1

5.3.2.1 Attempted Synthesis of Bromide (21)

With aldehyde **29** in hand, efforts were directed toward employing this hydroxyaldehyde in the approach to helicenes developed by Starý and coworkers. The first step was to convert the hydroxy group in **29** into a pseudo halide in preparation for subsequent Sonogashira chemistry.   Reaction of **29** with nonafluorobutylsulfonyl fluoride/NaH in DMF afforded nonaflate **34** in 75% yield (Scheme 5.10). Reaction of **34**

SCHEME 5.10 Attempted Synthesis of Bromide **21**
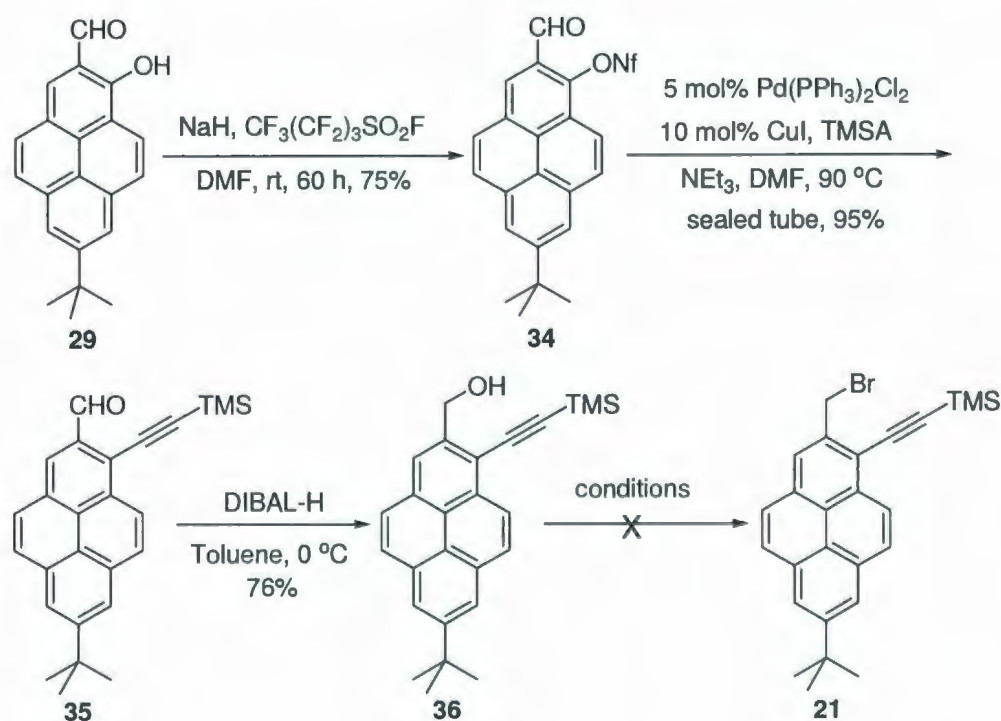
with trimethylsilylacetylene (TMSA) under standard Sonogashira conditions at 50 °C gave ynal **35** in 64% yield. When the reaction was performed in a sealed tube at 90 °C, the yield rose to 95% yield. Ynal **35** was then reduced with DIBAL-H to afford ynol **36** in 76% yield (Scheme 5.10).

The next task in the synthesis was to convert ynol **36** into the corresponding bromide and then use the newly formed functionality to attach an alkyne-containing side chain. In this vein, attempts were made to convert the alcohol into bromide **21**. Disappointingly, all of the methods that were attempted for this conversion met with failure (Table 5.1). On three occasions (Entries 1, 3 and 5), the starting material was totally consumed (tlc analysis) and a complex mixture of products formed. The most nonpolar product from this complex mixture was isolated as a single spot (tlc analysis) on two occasions (Entry 1 and 3), but the spectroscopic data (NMR, IR and MS) of this product were inconclusive. The only useful information from the ^{1}H NMR spectrum of this product was the absence of trimethylsilyl (TMS) group. This indicated that the TMS functionality is not stable towards the bromination conditions employed.

5.3.3 Approach 2

5.3.3.1 Attempted Synthesis of Triyne (23)

In order to circumvent the problem that occurred during bromination of ynol (**36**), the second retrosynthetic plan was considered, in which the coupling between the pyrene and naphthalene units was planned at an earlier stage in the synthesis. Thus, nonaflate **34**

TABLE 5.1 Attempted Synthesis of Bromide **21**
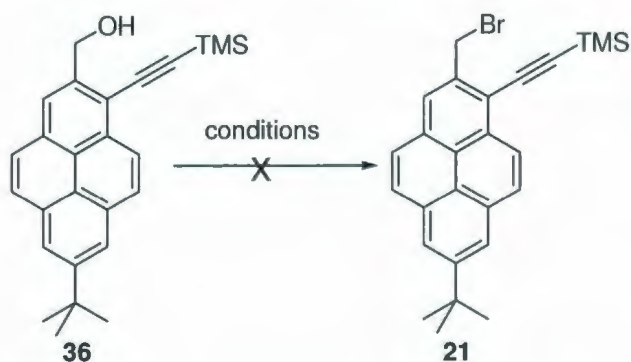
Entry	Reaction conditions	Result
1	PBr₃, CHCl₃, 0 °C, 2 h	complex mixture
2	CBr₄, PPh₃, THF, reflux, 3 h	no reaction
3	NBS, CHCl₃, rt, 3 h	complex mixture
4	CBr₄, PPh₃, pyridine, reflux, 2 h	no reaction
5	HBr/AcOH, 0 °C, 1 h	complex mixture

was subjected to Sonogashira reaction with naphthalene-containing diyne **25** at room tempera-ture to afford diynal **24** in 68% yield.

The stage was now set for the introduction of the alkyne-containing side chain to the pyrene moiety. In this direction, the addition of propargylmagnesium bromide to **24** was attempted, but the starting material, **24** was recovered (almost 100%) from this reaction (Scheme 5.11).

Indium-mediated reactions of the propargyl bromides have been reported to selectively afford either allenic or homopropargylic alcohols depending upon the choice

of the silyl protecting group.[23] This method also was unsuccessful (Scheme 5.12). The
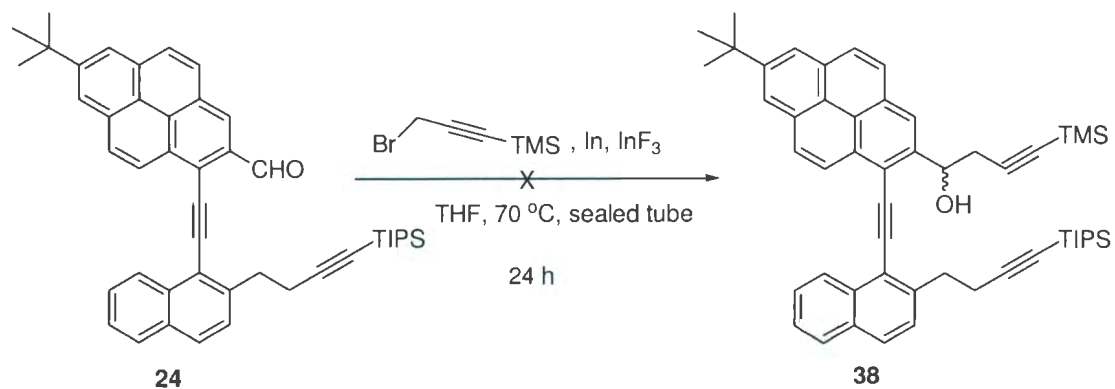
starting material **24** was recovered (almost 100%).

SCHEME 5.11 Attempted Synthesis of **29**
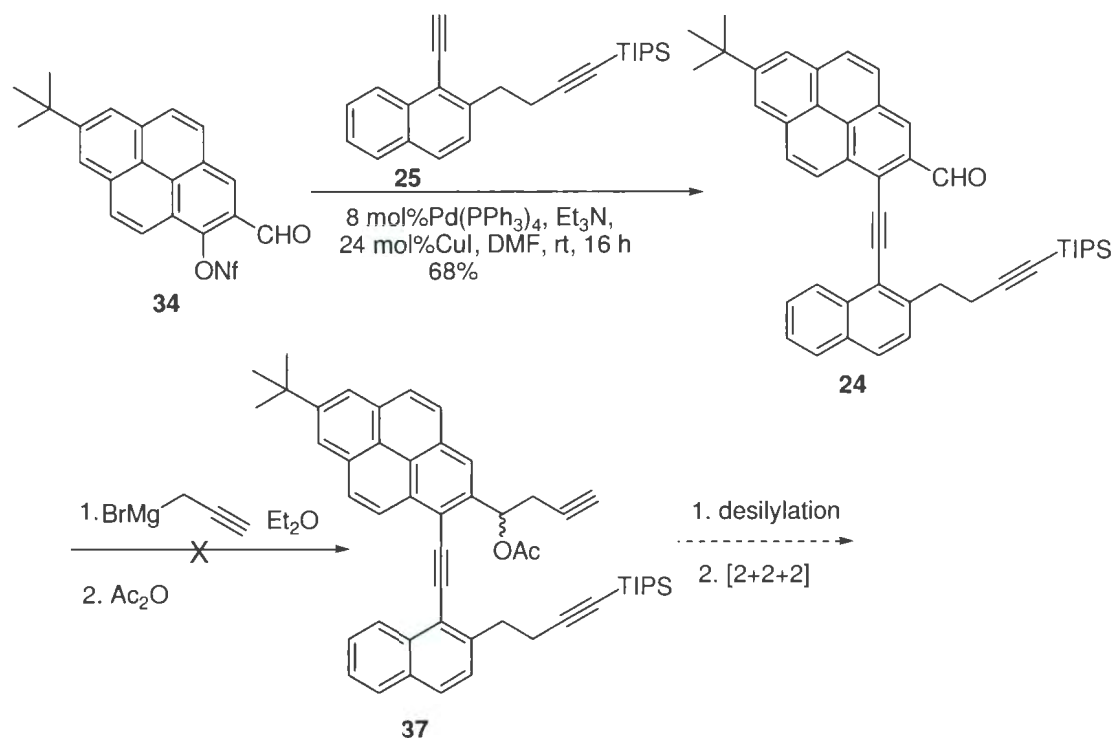
SCHEME 5.12 Attempted Synthesis of **38**

5.3.3.2 Synthesis of Enediyne 40

The presence of a propargyl group was desired for the crucial [2+2+2] cycloisomerization reaction. However, the reluctance of the aldehyde **24** to react with organopropargyl reagents raised a question whether the aldehyde was reactive towards such addition reactions. To find out whether this aldehyde could take part in similar reactions, it was reacted with allylmagnesium bromide. In fact, this reaction followed by protection of the resulting secondary alcohol as an acetate proceeded smoothly to afford protected enediyne **39** in 70% overall yield for the two steps (Scheme 5.13). It is not immediately obvious why the addition of allylmagnesiumbromide proceeds smoothly and

SCHEME 5.13 Synthesis of Enediyne **40**
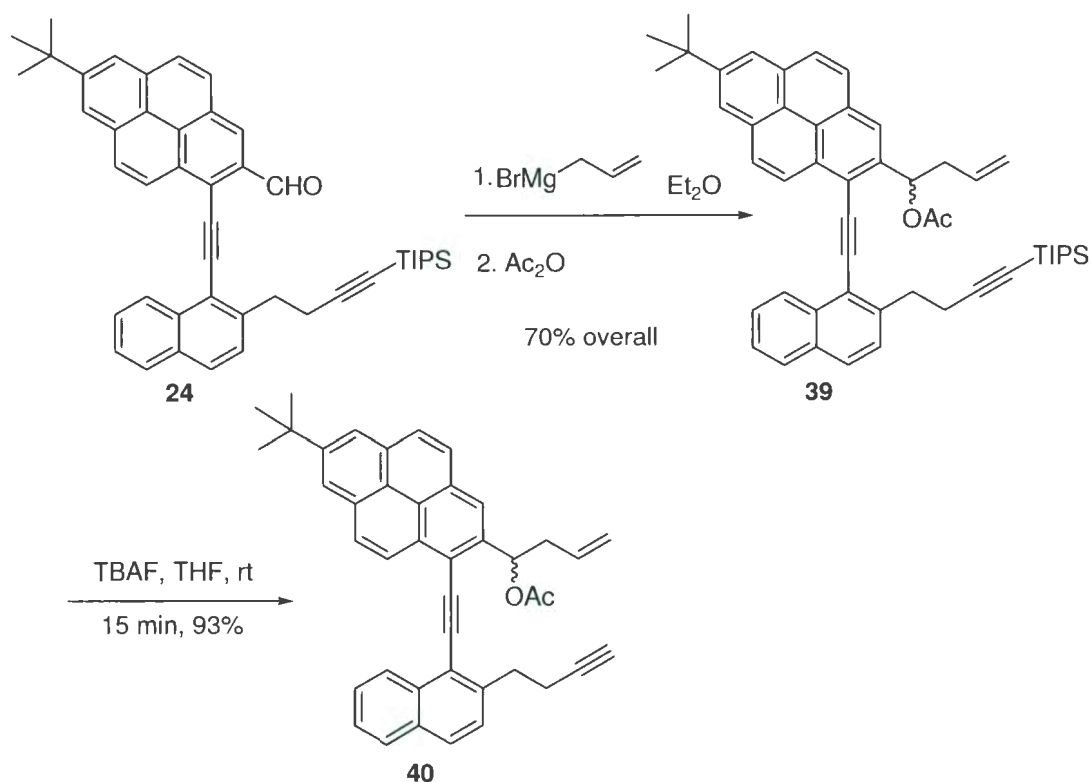
that of propargylmagnesiumbromide does not. Finally the silyl protecting group was removed through the action of TBAF on **39** to afford **40** in 93% yield.

5.3.3.3 Reaction of 40 Under [2+2+2] Cycloisomerization Conditions

At this stage, it was decided to explore the possibility of subjecting enediyne **40** to the [2+2+2] cycloisomerization conditions. Although the central ring that would be formed in this cycloisomerization would not be aromatic, it was hoped that the subsequent decomplexation (oxidative conditions) of the metal from the resulting cyclic diene might be accompanied by the aromatization of the central ring (Scheme 5.14).

When enediyne **40** was reacted with Jonas catalyst[24] at room temperature, the starting material was consumed after 15 minutes and two new products were observed (tlc analysis). However, the ^{1}H NMR spectra of both the crude reaction mixture and the single-spot fractions that were isolated by column chromatography were too complicated to assign any structure. Stirring a solution of these products (as a mixture) in THF open to air (1 hour at room temperature) did not show any reaction (tlc analysis). At this point, despite having made considerable progress, work aimed at the synthesis of **17** had to be discontinued due to a lack of time.

SCHEME 5.14 Attempted Synthesis of a Naphtho-fused [7]Helicene **17**

(Jonas Catalyst)
rt, 15 min

40

41

17

42
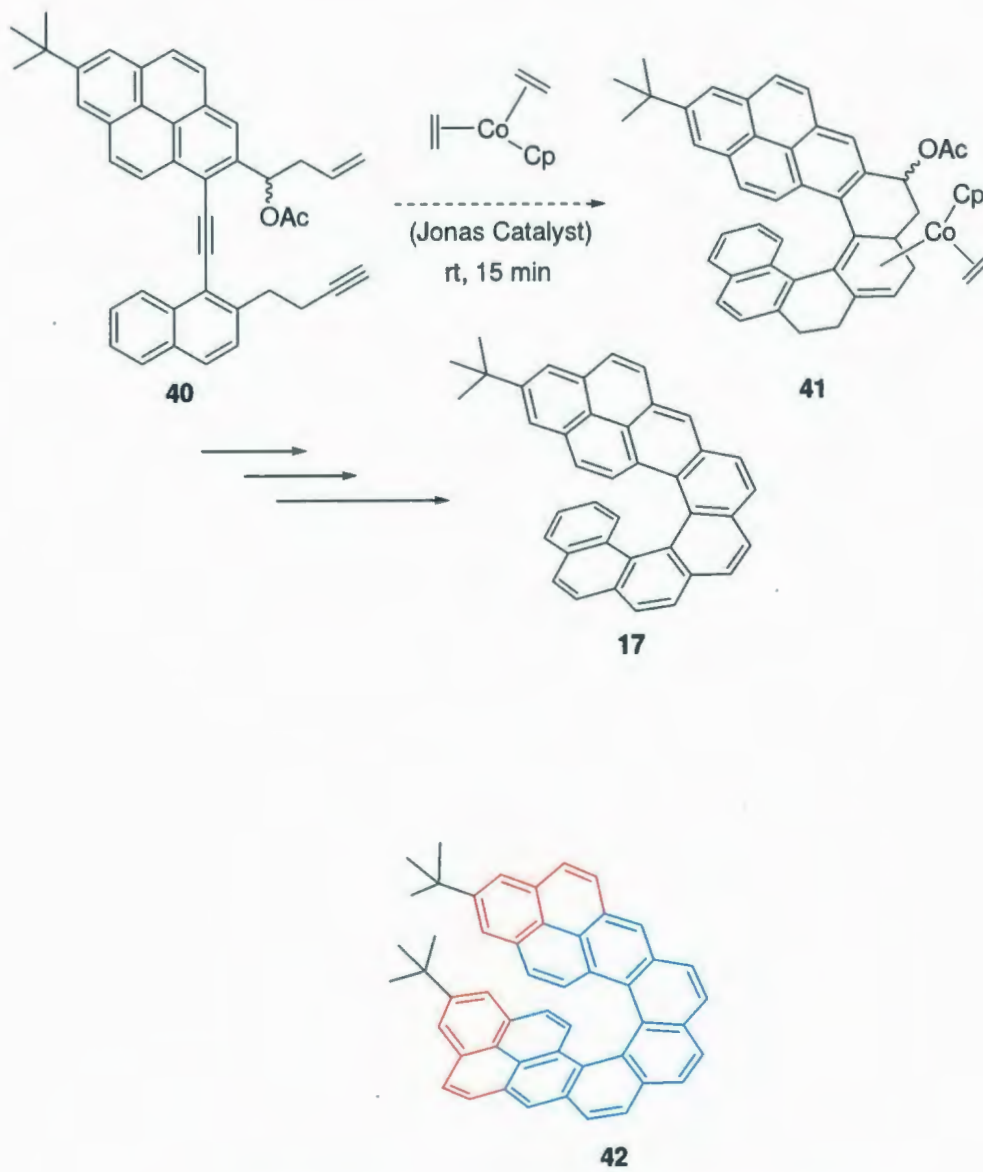
FIGURE 5.4 Interesting Target for Future Work

5.4 Conclusion

Although the synthesis of the target molecule **17** could not be achieved, various key intermediates for this synthesis were prepared, which may be useful in the future efforts toward the synthesis of **17** or its derivatives. Alternatively, other possibilities to prepare a suitable triyne from the nonaflate derivative **34** may be explored in future. A successful synthesis of **17** will mark the beginning of new type of synthetic targets such as **42** (Fig. 5.4), a helicene with two pyrene units.

5.5 Experimental

5.5.1 General Methods

All reactions were carried out using oven-dried glassware with inert gas protection, unless otherwise mentioned. For products **27, 30, 31, 32** and **33**, nitrogen was used as the inert atmosphere and for **24, 34, 35, 36, 39** and **40**, argon was used as the inert atmosphere. THF, diethyl ether and toluene were dried and distilled over sodium/benzophenone. Dichloromethane was dried and distilled over CaH_2. TMEDA was dried and distilled over KOH pellets and stored over 4 Å molecular sieves. DMF was dried over CaO and was freshly distilled for D*o*M reactions. All other chemicals, including solvents, were used as received without further purification. The concentration of *n*-BuLi in hexanes was determined prior to each use.

Thin layer chromatography (tlc) was performed on MN PolyGram precoated silica gel plates using 254 nm UV visualization. Flash chromatography was performed on silica gel columns. Melting points were recorded on Fisher Johns apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker AVANCE spectrometer at 500.133 MHz and 125.770 MHz, respectively. Peaks reported are relative to internal standards: TMS ($\delta = 0.00$) for ^1H and $CDCl_3$ ($\delta = 77.23$) for ^{13}C spectra. Reported multiplicities are apparent. All proton and carbon assignments are based on 2D experiments (COSY, HMQC and HMBC for **27, 30, 31, 32** and **33** and COSY, HMBC and HSQC for compounds **24, 34, 35, 36, 39** and **40**). Infrared spectra were obtained on Bruker Tensor 27 instrument using neat samples. Low-resolution mass spectra were obtained using using HP5970 GC/MSD or Agilent 1100 series LC/MS chromatographic

system and high-resolution mass spectra were obtained using Waters GCT Permier Micromass mass spectrometer.

5.5.2 Synthesis and Characterization

7-*tert*-Butylpyren-1-yl acetate (27) and 7-*tert*-butylpyren-1-ol (28)

27   **28**

I'
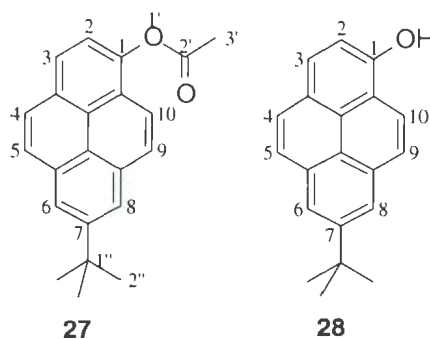
To a –10 °C slurry of AlCl₃ (3.77 g, 28.3 mmol) in dichloromethane (40 mL) was added

2-chloro-2-methylpropane (1.61 mL, 14.8 mmol) and the resulting mixture was stirred at

–10 °C for 15 min. To this mixture was added dropwise a clear, pale yellow solution of

26 (3.50 g, 13.5 mmol) in dichloromethane (40 mL) over a period of 15 min. The

resulting mixture was stirred at –10 °C for a further 1 h. Ice-cold 1 M HCl solution (50

mL) was then added to the reaction mixture and the biphasic mixture was transferred to a

separatory funnel. The layers were separated and the aqueous layer was extracted with

dichloromethane (2 × 20 mL). The combined organic layers were washed with brine (20

mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced

pressure and the residue was subjected to flash chromatography (10% ethyl

acetate/hexanes) to afford **27** (1.79 g, 42%) as an off-white solid and **28** (1.06 g, 29%) as

a brown gum. **27:** mp = 161-162 °C (trituration with ethyl acetate). $\delta_H(CDCl_3) = 8.24$ (d,

J = 1.9 Hz, 1H), 8.22 (d, J = 1.9 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H, H-3), 8.09 (d, J = 9.0 Hz, 1H), 8.05 (d, J = 9.1 Hz, 1H), 8.05-8.02 (m, 2H), 7.75 (d, J = 8.2 Hz, 1H, H-2), 2.54 (s, 3H, H-3'), 1.59 (s, 9H, H-2″) ppm; δ_C(CDCl$_3$) = 169.9 (C-2'), 149.8 (C-7), 144.4 (C-1), 131.2, 129.4, 128.2, 127.0, 126.9, 126.1, 125.3 (C-3), 124.3, 124.2, 122.0, 120.4, 120.3, 119.9, 119.6 (C-2), 36.2 (C-1″), 31.9 (C-2″), 21.8 (C-3') ppm; IR ν = 1759 (s), 1599 (w), 1558 (w), 1499 (m), 1459 (w), 1437 (w), 1416 (w), 1380 (m), 1367 (m), 1244 (w), 1216 (m), 1198 (s), 1167 (m), 1152 (m), 1143 (m), 1131 (w), 1172 (w), 1069 (m), 1011 (w) cm^{-1}; GC/MS m/z (relative intensity) = 316 (M$^+$, 17), 274 (100), 259 (30), 218 (16); HRMS [M$^+$] calcd for C$_{22}$H$_{20}$O$_2$ 316.1463, found 316.1457. **28:** δ_H(CDCl$_3$) = 8.28-7.88 (br m, 7H), 7.52-7.35 (br m, 1H), 5.48 (s, 1H, exchangeable with D$_2$O), 1.57 (s, 9H) ppm, GC/MS m/z (relative intensity) = 274 (M$^+$, 100), 259 (51), 218 (28), 189 (21), 115 (27). Due to very broad peaks in ^{1}H NMR, this compound was not fully characterized. It was used in the next step and the product of that reaction was fully characterized.

**7-*tert*-Butylpyren-1-ol (28)**

28
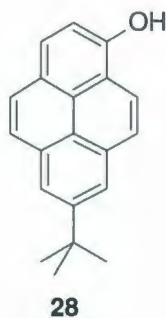
To a clear, brown room temperature solution of **27** (1.79 g, 5.66 mmol) in chloroform:methanol (1:1) (50.0 mL) was added K$_2$CO$_3$ (0.860 g, 6.22 mmol). The

reaction mixture was stirred open to air at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (60 mL). This solution was washed with 1 M HCl solution (2 × 25 mL), washed with brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford **28** as a brown gum (1.54 g, 99%).

7-*tert*-Butylpyren-1-yl dimethylcarbamate (30)

30
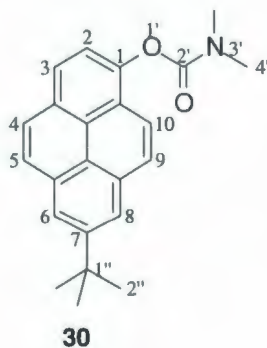
To a clear, brown solution of **28** (0.19 g, 0.69 mmol) in chloroform (7.0 mL) were added DMAP (0.017 g, 20 mol%), triethylamine (0.11 mL, 0.76 mmol) and *N,N*-dimethylcarbamoyl chloride (0.07 mL, 0.8 mmol) and the reaction mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and chloroform (10 mL) was added. The resulting mixture was washed with 1 M HCl solution (2 × 20 mL), washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was triturated with ether to afford **30** (0.076 g, 32%) as a pale yellow solid. The mother liquor was filtered through a short (4 cm × 2

358

cm) silica gel column (20% ethyl acetate) to afford **30** (0.16 g, 68%) as a pale yellow

solid. Combined yield = 0.24 g (100%). mp = 178-179 °C (trituration with ethyl acetate).

δ_H(CDCl$_3$) = 8.19 (m, 2H), 8.11-8.04 (m, 3H), 7.98 (m, 2H), 7.79 (d, J = 8.1 Hz, 1H, H-

2), 3.39 (s, 3H, H-4'), 3.08 (s, 3H, H-4'), 1.58 (s, 9H, C-2'') ppm; δ_C(CDCl$_3$) = 155.5 (C-

2'), 149.7 (C-7), 145.4 (C-1), 131.4, 131.3, 129.1, 128.4, 127.4, 127.3, 125.9, 125.2,

123.6, 123.3, 122.9, 122.6, 120.7, 120.1 (C-2), 37.3 (C-4'), 37.1 (C-4'), 35.6 (C-1''), 32.3

(C-2'') ppm; MS (APCI) m/z (relative intensity) = 346 (M$^+$+1, 100), 274 (48); HRMS

[M$^+$] calcd for C$_{23}$H$_{23}$NO$_2$ 345.1729, found 345.1723.

7-*tert*-Butyl-1-hydroxy-*N*,*N*-dimethylpyrene-2-carboxamide (31)


31
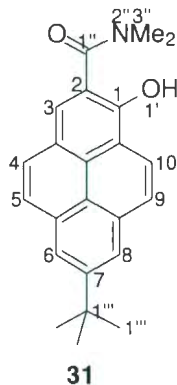
To a –78 °C mixture of TMEDA (0.040 mL, 0.28 mmol) and *n*-BuLi (1.4 M solution in

hexanes, 0.20 mL, 0.28 mmol) in THF (1.0 mL) was added a clear, pale yellow solution

of **30** (0.087 g, 0.25 mmol) in THF (2.0 mL). The resulting cloudy red solution was

stirred at –78 °C for 2 h. DMF (0.08 mL, 1.00 mmol) was added and the reaction mixture

was stirred at –78 ºC for another 2 h. Cold saturated NH_4Cl solution (5 mL) was added to the reaction mixture carefully. The solvent was removed under reduced pressure and the residue was diluted with cold water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (0-10% ethyl acetate/hexanes) to afford **31** as a yellow solid (0.048 g, 55%). mp = 198-199 ºC (trituration with ethyl acetate). $\delta_H(CDCl_3)$ = 10.96 (s, 1H, H-1′), 8.48 (d, J = 8.3 Hz, 1H), 8.15-8.11 (m, 2H), 8.04-8.02 (m, 2H), 7.85 (m, 2H), 3.32 (s, 6H, H-3″), 1.56 (s, 9H, H-2‴) ppm; $\delta_C(CDCl_3)$ = 173.1 (C-1′), 154.1 (C-1), 150.4 (C-7), 132.4, 132.1, 127.3, 127.2, 127.1, 125.7 (C-3), 124.2, 123.1, 122.8, 121.90, 121.88, 120.2, 113.9, 38.4 (C-3″), 35.5 (C-1‴), 32.1 (C-2″) ppm (one carbon signal fewer than expected); IR ν = 3629 (w), 1684 (s), 1653 (m), 1617 (m), 1560 (m), 1499 (m), 1477 (w), 1440 (w), 1414 (m), 1390 (w), 1375 (m), 1353 (m), 1250 (s), 1190 (s), 1127 (m), 1088 (w), 1059 (m) cm^{-1}; MS (APCI) m/z (relative intensity) = 346 (M^++1, 100); HRMS [M^+] calcd for $C_{23}H_{23}NO_2$ 345.1729, found 345.1727.

7-*tert*-Butyl-1-(methoxymethoxy)pyrene (32)
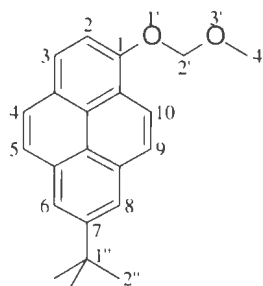
32

Method 1: NaH (60% suspension in mineral oil, 0.48 g, 9.72 mmol) was washed with n-hexane (2 × 10 mL) in a 3-necked round-bottomed flask. THF (20.0 mL) was added and the resulting suspension was cooled in an ice bath. A clear, brown solution of 7-*tert*-butylpyren-1-ol (**28**) (2.21 g, 8.10 mmol) in THF (50 mL) was then added and the reaction mixture was stirred for 15 min at 0 °C. Methoxymethyl chloride (0.740 mL, 9.72 mmol) was then added and the reaction mixture was stirred at 0 °C for 3 h. A few drops of methanol were added to the reaction mixture and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (80 mL) and the resulting solution was washed with cold water (40 mL), brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (0-2.5% ethyl acetate/hexanes) to afford **32** as a pale yellow gum (2.21 g, 89%). $\delta_H(CDCl_3)$ = 8.42 (d, J = 9.4 Hz, 1H), 8.16 (br s, 1H), 8.15 (br s, 1H), 8.05 (d, J = 8.6 Hz, 1H, H-3), 8.03 (d, J = 9.6 Hz, 1H), 7.94 (d, J = 9.4 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.74 (d, J = 8.6 Hz, 1H, H-2), 5.52 (s, 2H, H-2'), 3.61 (s, 3H, H-

4′), 1.57 (s, 9H, H-2″) ppm; δ_C(CDCl$_3$) = 151.3 (C-1), 149.4 (C-7), 131.64, 131.59, 127.3, 127.1, 126.3, 126.0, 125.9, 125.5, 123.4, 122.1, 121.8, 121.2, 121.0 (C-2), 111.9, 95.7 (C-2′), 56.6 (C-4′), 35.4 (C-1″), 32.1 (C-2″) ppm; GC/MS m/z (relative intensity) = 318 (M$^+$, 39), 273 (100), 243 (11); HRMS [M$^+$] calcd for C$_{22}$H$_{22}$O$_2$ 318.1620, found 318.1629.

Method 2: To a clear, brown, 5 °C solution of **28** (1.26 g, 4.59 mmol) in THF (50 mL) were added triethylamine (0.96 mL, 6.89 mmol) and methoxymethyl chloride (0.520 mL, 6.89 mmol). The reaction was stirred at room temperature for 48 h and then heated to reflux for a further 48 h. The reaction mixture was allowed to cool to room temperature and then cold water (30 mL) was added. The biphasic mixture was transferred to a separatory funnel and the two layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated under reduced pressure and the residue was subjected to flash chromatography (0-5% ethyl acetate/hexanes) to afford **32** as a pale yellow gum (1.08 g, 68%).

7-*tert*-Butyl-1-(methoxymethoxy)pyrene-2-carbaldehyde (33)

33
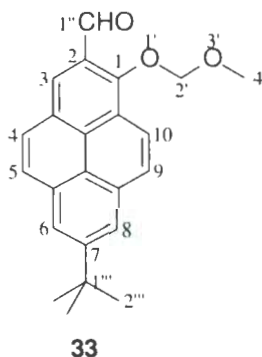
Method 1: To a clear, pale yellow, −20 °C solution of **32** (1.90 g, 5.97 mmol) and TMEDA (1.08 mL, 7.16 mmol) in THF (50.0 mL) was added *n*-BuLi (0.94 M solution in hexanes, 7.62 mL, 7.16 mmol). The resulting deep red solution was stirred at −20 °C for 1 h. DMF (0.920 mL, 11.9 mmol) was then added and stirred was continued at −20 °C for 1.5 h. Cold saturated NH$_4$Cl solution (20 mL) was then added to the reaction mixture carefully. The solvent was removed under reduced pressure and the residue was diluted with cold water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was subjected to flash chromamtography (0-10% ethyl acetate/hexanes) to afford **33** as a yellow solid (1.44 g, 70%). mp = 132-134 °C; δ_H(CDCl$_3$) = 10.74 (s, 1H, H-1″), 8.53 (s, 1H, H-3), 8.31 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 1.5 Hz, 1H), 8.18 (d, *J* = 1.5 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.97 (d, *J* = 9.1 Hz, 1H), 7.94 (d, *J* = 9.4 Hz, 1H), 5.37 (s, 2H, H-2′), 3.67 (s, 3H, H-4′),

1.57 (s, 9H, H-2′′′) ppm; δ$_C$(CDCl$_3$) = 191.3 (C-1″), 154.4 (C-1), 151.3 (C-7), 132.1, 132.0, 129.3, 128.7 (C-3), 128.0, 127.9, 127.8, 126.6, 124.7, 123.9, 123.2, 122.9, 122.8, 121.4, 102.6 (C-2′), 58.5 (C-4′), 35.6 (C-1′′′), 32.0 (C-2′′′) ppm; GC/MS *m/z* (relative intensity) = 346 (M$^+$, 24), 316 (13), 300 (100), 286 (39), 273 (23), 257 (16), 243 (18), 189 (14); HRMS [M$^+$] calcd for C$_{23}$H$_{22}$O$_3$ = 346.1569, found = 346.1563.

Method 2: To a clear, pale yellow –20 °C solution of **32** (0.32 g, 1.0 mmol) and TMEDA (0.18 mL, 1.2 mmol) in THF (10 mL) was added *n*-BuLi (0.94 M solution in hexanes, 1.3 mL, 1.2 mmol). The resulting deep red solution was stirred at –20 °C for 1 h and *N*-methylformanilide 0.25 mL, 2.0 mmol) was added. Stirred was continued at –20 °C for a further 1.5 h and then cold saturated NH$_4$Cl solution (5 mL) was added carefully. The solvent was removed under reduced pressure and the residue was diluted with cold water (10 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was subjected to flash chromamtography (0-10% ethyl acetate/hexanes) to afford **33** as a yellow solid (0.24 g, 70%).

Method 3: To a clear, pale yellow –20 °C solution of **32** (0.32 g, 1.0 mmol) and TMEDA (0.18 mL, 1.2 mmol) in diethyl ether (10 mL) was added *n*-BuLi (0.94 M solution in hexanes, 1.3 mL, 1.2 mmol). The resulting deep red, cloudy solution was stirred at –20 °C for 1 h and DMF (0.15 mL, 2.0 mmol) was then added. Stirring was continued at –20 °C for a further 1.5 h. and cold saturated NH$_4$Cl solution (5 mL) was added carefully. Diethyl ether (5 mL) was then added and the resulting biphasic mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with

diethyl ether (2 × 5 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was subjected to flash chromamtography (0-10% ethyl acetate/hexanes) to afford **33** as a yellow solid (0.21 g, 62%).

### 7-*tert*-Butyl-1-hydroxypyrene-2-carbaldehyde (29)

29
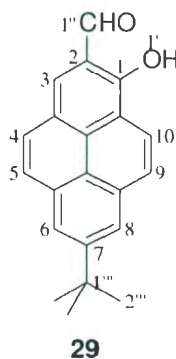
A yellow suspension of **33** (1.14 g, 3.00 mmol) in methanol:37% HCl solution (2:1) (60 mL) was stirred open to air at room temperature for 16 h. The solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane (80 mL). The solution was washed with saturated NaHCO$_3$ solution (40 mL) and washed with brine (40 mL). The organic layer was then dried over anhydrous Na$_2$SO$_4$ and the solvent was removed under reduced pressure to afford **29** as a yellow solid (0.902 g, 100%).

mp = 191-192 °C (dichloromethane). δ_H(CDCl$_3$) = 11.93 (s, 1H, H-1'), 10.29 (s, 1H, H-1"), 8.48 (s, 1H, H-3), 8.20 (d, J = 8.4 Hz, 1H), 8.15 (s, 1H), 8.12 (s, 1H), 8.05 (d, J = 8.6

Hz, 1H), 7.90 (d, J = 9.2 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H), 1.57 (s, 9H, H-2‴) ppm;

δ_C(CDCl$_3$) = 197.1 (C-1″), 155.8 (C-1), 151.4 (C-7), 132.9, 132.5, 129.4, 128.3 (C-3) ,

127.2, 127.1, 126.0, 124.0, 122.8 (C-2), 122.3, 122.0, 121.3, 119.3, 116.7, 35.3 (C-1‴),

31.7 (C-2‴) ppm; MS (APCI) m/z (relative intensity) = 303 (M$^+$+1, 24), 302 (100);

HRMS [M$^+$] calcd for C$_{21}$H$_{18}$O$_2$ = 302.1307, found = 302.1309.

7-*tert*-Butyl-2-formylpyrene-1-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (34)

34
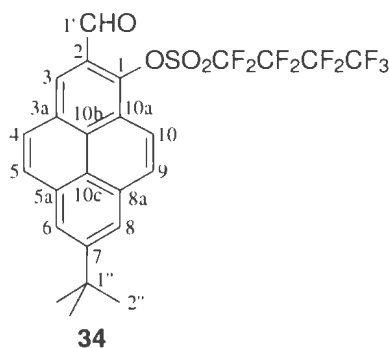
To a 0 °C suspension of NaH (80% dispersion in mineral oil, 0.12 g, 4.0 mmol, washed once with n-hexane (10 mL)) in DMF (10 mL) was added a clear yellow solution of 7-*t*-butyl-2-formyl-1-hydroxypyrene (**29**) (0.60 g, 2.0 mmol) in DMF (10 mL) and the resulting mixture was stirred at 0 °C for 1.5 h. Nonafluorobutanesulfonyl fluoride (0.46 mL, 2.6 mmol) was then added and the resulting mixture was stirred at room temperature for 62 h. The solvent was removed under reduced pressure (10 mbar, 60 °C) and the residue was subjected to flash chromatography (0-2.5% ethyl acetate/hexanes) to afford **34** as a yellow solid (0.87 g, 75%). mp = 103-104 °C; δ_H(CDCl$_3$) = 10.66 (s, 1H, H-1′), 8.72 (s, 1H, H-3), 8.36 (d, J = 9.5 Hz, 1H, H-10), 8.35 (m, 2H, H-6 and H-8), 8.29 (d, J =

9.5 Hz, 1H, H-9), 8.21 (d, J = 9.0 Hz, 1H, H-5), 8.16 (d, J = 9.1 Hz, 1H, H-4), 1.60 (s, 9H, H-2″) ppm; δ_C(CDCl$_3$) = 187.6 (d, C-1′), 152.0 (s, C-7), 141.5 (s, C-1), 131.5 (s, C-5a), 131.2 (s, C-8a), 130.7 (d, C-9), 130.5 (s, C-3a), 129.9 (d, C-5), 128.5 (s, C-10b), 127.2 (d, C-4), 125.8 (s, C-10a), 124.6 (d, C-3), 124.44 (d, C-6), 124.42 (s, C-2), 124.1 (d, C-8), 121.8 (s, C-10c), 119.9 (d, C-10), 35.5 (s, C-1″), 31.8 (q, C-2″) ppm (chemical shifts for CF$_2$CF$_2$CF$_2$CF$_3$ are not given because unambiguous assignment was not possible due to strong ^{13}C,^{19}F splitting); IR ν = 1720 (s), 1696 (s), 1652 (w), 1635 (w), 1606 (w), 1592 (w), 1565 (m), 1478 (w), 1470 (w), 1461 (w), 1429 (m), 1398 (m), 1369 (m), 1352 (m), 1285 (m), 1243 (s), 1146 (s), 1089 (w), 1032 (w), 1009 (w) cm^{-1}; MS (EI) m/z (relative intensity) = 584 (M$^+$, 26), 583 (M$^+$-1, 100), 301 (31), 299 (27). HRMS [M$^+$] calcd for C$_{25}$H$_{17}$O$_4$F$_9$S 584.0704, found 584.0696.

7-*tert*-Butyl-1-((trimethylsilyl)ethynyl)pyrene-2-carbaldehyde (35)

35
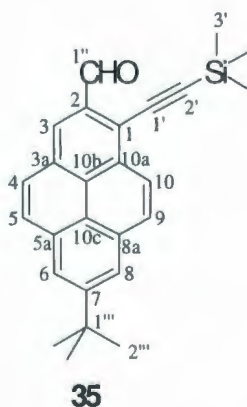
A Schlenk flask was charged with PdCl$_2$(PPh$_3$)$_2$ (32 mg, 0.046 mmol, 5 mol%) and CuI (18 mg, 0.092 mmol, 10 mol%) and kept under argon. Through a septum, a clear yellow

solution of **34** (0.54 g, 0.92 mmol) in DMF (20 mL) was added followed by the addition of triethylamine (0.64 mL, 4.6 mmol) and trimethylsilylacetylene (0.16 mL, 1.1 mmol). The reaction flask was sealed with a teflon screw cap and the reaction mixture was heated at 90 °C for 2 h. The solvent was removed under reduced pressure (15 mbar, 60 °C) and the residue was adsorbed on silica gel and subjected to flash chromatography (0-5% ethyl acetate/hexanes) to afford **35** as a yellow solid (309 mg, 87%). mp = 124-125 °C; δ_H(CDCl$_3$) = 11.01 (s, 1H, H-1″), 8.64 (s, 1H, H-3), 8.63 (d, J = 9.1 Hz, 1H, H-10), 8.29 (d, J = 1.8 Hz, 1H, H-8), 8.26 (d, J = 1.8 Hz, 1H, H-6), 8.21 (d, J = 9.1 Hz, 1H, H-9), 8.10 (d, J = 9.1 Hz, 1H, H-5), 8.07 (d, J = 9.1 Hz, 1H, H-4), 1.60 (s, 9H, H-2‴), 0.43 (s, 9H, H-3′) ppm; δ_C(CDCl$_3$) = 193.2 (d, C-1″), 151.1 (s, C-7), 132.8 (s, C-2), 132.6 (s, C-10a), 131.8 (s, C-5a), 131.7 (s, C-8a), 130.5 (s, C-3a), 129.5 (d, C-9 and d, C-5, degenerate peaks), 127.9 (d, C-4), 127.0 (s, C-10b), 125.2 (d, C-10), 123.6 (d, C-6), 123.5 (d, C-8), 122.5 (d, C-3), 122.1 (s, C-10c), 120.4 (s, C-1), 108.1 (s, C-1′), 99.2 (s, C-2′), 35.4 (s, C-1‴), 31.8 (q, C-2‴), 0.03 (q, C-3′) ppm; IR ν = 3301 (w), 2145 (m), 1692 (s), 1670 (m), 1252 (m), 1633 (w), 1626 (w), 1588 (m), 1563 (m), 1546 (m), 1462 (w), 1383 (m); MS (EI) m/z (relative intensity) = 382 (M$^+$, 94), 367 (69), 256 (22), 72 (66), 57 (100). HRMS [M$^+$] calcd for C$_{26}$H$_{26}$OSi 382.1753, found 382.1759.

(7-*tert*-Butyl-1-((trimethylsilyl)ethynyl)pyrene-2-yl)methanol (36)

36
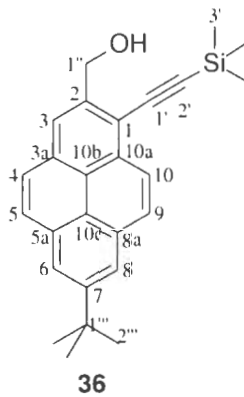
To a clear, yellow solution of **35** (0.36 g, 0.94 mmol) in toluene (30 mL) was added DIBAL-H (1.5 M solution in toluene, 0.75 mL, 1.1 mmol) over 2 min at 0 °C under an argon atmosphere. The reaction mixture was stirred at room temperature for 16 h. Saturated NaCl solution (1.0 mL) was added carefully and the solvent was removed under reduced pressure. Saturated NaCl solution (20 mL) was added to the residue and the resulting mixture was extracted with dichloromethane (1 × 20 mL and 2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography (0-10% ethyl acetate/hexanes) to afford **36** as a yellow solid (0.31 g, 85%). mp = 148-149 °C; δ_H(CDCl$_3$) = 8.55 (d, J = 9.1 Hz, 1H, H-10), 8.26 (d, J = 1.8 Hz, 1H, H-8), 8.24 (d, J = 1.8 Hz, 1H, H-6), 8.16 (d, J = 9.1 Hz, 1H, H-9), 8.09 (d, J = 9.2 Hz, 1H, H-5), 8.08 (s, 1H, H-3), 8.01 (d, J = 9.2 Hz, 1H, H-4), 5.70 (s, 2H, H-1″), 1.59 (s, 9H, H-2‴), 0.40 (s, 9H, H-3′) ppm; δ_C(CDCl$_3$) = 149.6 (s, C-7), 135.1 (s, C-2), 132.4 (s, C-10a), 131.0 (s, C-5a), 130.8 (s, C-3a and s, C-8a, degenerate peaks), 129.0 (d, C-9), 128.9 (d, C-5), 127.0

(d, C-4), 125.4 (d, C-10), 124.2 (d, C-3), 123.9 (s, C-10b), 123.1 (s, C-6 and s, C-8, degenerate peaks), 122.3 (s, C-10c), 116.7 (s, C-1), 105.7 (s, C-1'), 101.0 (s, C-2'), 65.8 (t, C-1''), 35.3 (s, C-1'''), 31.9 (q, C-2'''), 0.12 (q, C-3') ppm; HRMS [M^++CH$_3$CN+1] calcd for $C_{28}H_{32}NOSi$ (M^++H$^+$CH$_3$CN) 426.1796, found 426.2005.

7-*tert*-Butyl-1-((2-(4-triisopropylsilyl)but-3-ynyl)naphthalene-1-yl)ethynyl)pyrene-2-carbaldehyde (24)

24
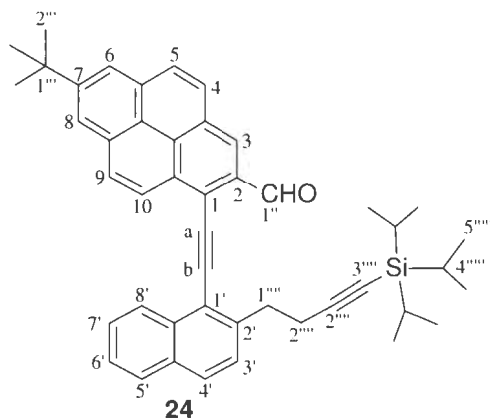
To a Schlenk flask containing naphthalene-based diyne **25** (0.34 g, 0.94 mmol) under an argon atmosphere was added Pd(PPh$_3$)$_4$ (38 mg, 0.033 mmol, 8 mol%), CuI (19 mg, 0.098 mmol, 24 mol%) and DMF (2.0 mL). To this mixture was added triethylamine (0.11 mL, 0.82 mmol). A clear, yellow solution of nonaflate **34** (0.24 g, 0.41 mmol) in DMF (8.0 mL) was then added to the resulting brown solution. The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography to afford **24** (0.16 g, 68%) as a

yellow oil. $\delta_H(\text{CDCl}_3)$ = 11.27 (s, 1H, H-1″), 8.92 (d, J = 9.1 Hz, 1H, H-10), 8.76 (s, 1H, H-3), 8.62 (dq, J = 8.4, 0.9 Hz, 1H, H-8′), 8.31 (d, J = 9.1 Hz, 1H, H-9), 8.31 (d, J = 1.8 Hz, 1H, H-8), 8.30 (d, J = 1.8 Hz, 1H, H-6), 8.16 (s, 2H, H-5 and H-4), 7.91 (ddt, J = 8.3, 1.3, 0.7 Hz, 1H, H-5′), 7.88 (br d, J = 8.4 Hz, 1H, H-4′), 7.80 (d, J = 8.4 Hz, 1H, H-3′), 7.68 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H, H-7′), 7.56 (ddd, J = 8.0, 1.3, 0.7 Hz, 1H, H-6′), 3.53 (t, J = 7.4 Hz, 2H, H-1‴′), 2.89 (t, J = 7.4 Hz, 2H, H-2‴′), 1.61 (s, 9H, H-2‴), 0.98-0.95 (m, 21H, H-5‴′ and H-6‴′) ppm; $\delta_C(\text{CDCl}_3)$ = 192.7 (d, C-1″), 151.2 (s, C-7), 142.4 (s, C-2′), 133.8 (s, C-8′a), 132.64 (s, C-2), 132.60 (s, C-10a), 132.1 (s, C-4′a), 132.0 (s, C-5a), 131.8 (s, C-8a), 130.6 (s, C-3a), 129.8 (d, C-9), 129.5 (d, C-5), 129.2 (d, C-4′), 128.4 (d, C-5′), 127.9 (d, C-4), 127.6 (d, C-3′), 127.35 (d, C-7′), 127.31 (s, C-10b), 126.1 (d, C-6′ and C-8′, degenerate peaks), 125.3 (d, C-10), 123.7 (d, C-8), 123.5 (d, C-6), 123.2 (d, C-3), 122.3 (s, C-10c), 120.7 (s, C-1), 118.9 (s, C-1′), 107.5 (s, C-3‴′), 98.4 (s, C-b), 93.3 (s, C-a), 81.6 (s, C-4‴′), 35.4 (s, C-1‴), 35.0 (t, C-1‴′), 31.8 (q, C-2‴), 21.6 (t, C-2‴′), 18.5 (q, C-6‴′), 11.2 (s, C-5‴′) ppm; IR ν = 3056 (w), 2963 (s), 2865 (s), 2194 (w), 2170 (w), 1691 (s), 1633 (w), 1624 (w), 1605 (w), 1589 (m), 1545 (w), 1508 (w), 1495 (w), 1481 (w), 1464 (m), 1432 (w), 1315 (w), 1396 (m), 1392 (w), 1382 (w), 1364 (w), 1102 (w), 1080 (w), 997 (w), 920 (w), 884 (s), 679 (m), 661 (m), 615 (w); MS (EI) m/z (relative intensity) = 645 (M$^+$, 85), 631 (90), 606 (100), 605 (80); HRMS [M$^+$] calcd for $C_{46}H_{49}OSi$ 645.3547, found 645.3544.

1-(7-*tert*-Butyl-1-((2-(4-triisopropylsilyl)but-3-ynyl)naphthalene-1-yl)ethynyl)pyrene-2-yl)but-3-enyl acetate (39)
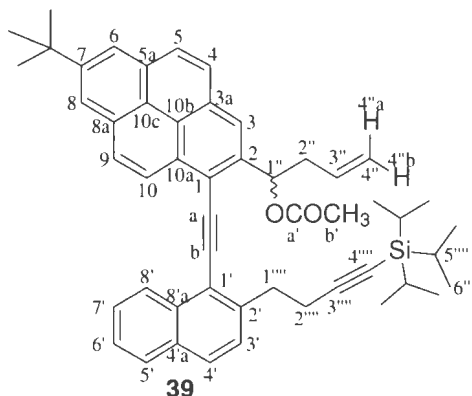
To a clear, orange solution of **24** (0.14 mg, 0.21 mmol) in THF (5.0 mL) at 0 °C under an argon atmosphere was added allylmagnesium bromide (0.42 mL 1.0 M solution in diethyl ether, 0.42 mmol). The resulting clear yellow solution was stirred at room temperature for 10 min and acetic anhydride (0.48 mL, 5.0 mmol) was added. The reaction mixture was then stirred at room temperature for 12 h. Cold water (10 mL) and ethyl acetate (10 mL) were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography (0-5% diethyl ether/hexanes) to afford **39** as a pale yellow oil (0.13 g, 85%). $\delta_H(CDCl_3)$ = 8.83 (d, J = 9.1 Hz, 1H, H-10), 8.77 (dq, J = 8.4, 0.9 Hz, 1H, H-8'), 8.25 (d, J = 9.1 Hz, 1H, H-9), 8.26 (d, J = 1.8 Hz, 1H, H-8), 8.25 (d, J = 1.8 Hz, 1H, H-6), 8.24 (s, 1H, H-3), 8.11 (d, J

= 9.1 Hz, 1H, H-5), 8.06 (d, J = 9.1 Hz, 1H, H-4), 7.89 (ddt, J = 8.1, 1.4, 0.7 Hz, 1H, H-5′), 7.84 (d, J = 8.4 Hz, 1H, H-4′), 7.67 (ddd, J = 8.1, 6.8, 1.4 Hz, 1H, H-7′), 7.61 (d, J = 8.4 Hz, 1H, H-3′), 7.54 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H, H-6′), 7.03 (dd, J = 8.0, 5.0 Hz, 1H, H-1″), 5.89 (dddd, 17.2, 10.2, 7.3, 6.5 Hz, 1H, H-3″), 5.10 (dq, 17.2, 1.5 Hz, 1H, H-4″a), 5.06 (ddt, J = 10.2, 1.8, 1.1 Hz, 1H, H-4″b), 3.58-3.51 (m, 2H, H-1″″″), 3.01 (ddt, J = 14.8, 6.5, 1.4 Hz, 1H, H-2″), 2.93 (dtt, J = 14.8, 7.5, 1.2 Hz, 1H, H-2″), 2.90 (t, J = 7.3 Hz, 2H, H-2″″″), 2.22 (s, 3H, H-b″), 1.60 (s, 9H, H-2″′), 1.01-0.99 (m, 21H, H-5″″″ and H-6″″″) ppm; δ_C(CDCl$_3$) = 170.1 (s, C-a′), 149.5 (s, C-7), 141.9 (s, C-2′), 139.4 (s, C-2), 133.8 (s, C-8′a), 133.4 (d, C-3″), 132.2 (s, C-10a), 132.1 (s, C-4′a), 131.02 (s, C-3a), 130.96 (s, C-8a), 130.8 (s, C-5a), 129.2 (d, C-9), 128.8 (d, C-5), 128.6 (d, C-4′), 128.2 (d, C-5′), 127.8 (d, C-3′), 127.13 (d, C-4), 127.07 (d, C-7′), 126.5 (d, C-8′), 125.9 (d, C-6′), 125.5 (d, C-10), 123.9 (s, C-10b), 123.1 (d, C-8), 123.0 (d, C-6), 122.4 (s, C-10c), 121.8 (d, C-3), 119.5 (s, C-1′), 118.2 (t, C-4″), 115.8 (s, C-1), 108.0 (s, C-3″″″), 96.9 (s, C-b), 95.0 (s, C-a), 81.4 (s, C-4″″″), 74.1 (d, C-1″), 41.2 (t, C-2″), 35.3 (s, C-1″″″), 35.0 (t, C-1″″″), 31.9 (q, C-2″′), 21.6 (t, C-2″″″), 21.3 (q, C-b″), 18.6 (q, C-6″″″), 11.3 (d, C-5″″″) ppm; IR ν = 3078 (w), 3054 (w), 2964 (s), 2866 (s), 2170 (w),1737 (s), 1642 (w), 1602 (w), 1590 (w), 1566 (w), 1508 (w), 1494 (w), 1478 (w), 1463 (m), 1431 (w), 1417 (w), 1395 (w), 1380 (m), 1371 (m), 1364 (m), 1240 (s), 1155 (w), 1026 (m), 996 (m), 884 (s), 867 (w), 815 (m) cm^{-1}; MS (EI) m/z (relative intensity) = 728 (M$^+$, 10), 662 (M$^+$-56, 100), 316 (38); HRMS [M$^+$] calcd for C$_{51}$H$_{56}$O$_2$Si 728.4050, found 728.4069.

1-(1-((2-(But-3-ynyl)naphthalen-1-yl)ethynyl)-7-*tert*-butylpyren-2-yl)but-3-enyl acetate (40)

40
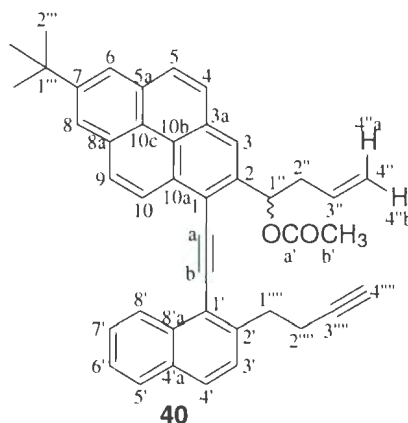
To a clear, yellow room temperature solution of **39** (0.12 g, 0.17 mmol) in THF (3.0 mL) was added TBAF (0.914 M solution in THF, 0.22 mL, 0.20 mmol) under an argon atmosphere. The resulting clear, orange solution was stirred at room temperature for 15 min. The solvent was removed under reduced pressure (at 25-28 °C). The residue was purified by filtration through a short (5 cm × 2 cm) silica gel column (5% diethyl ether/hexane) to afford **40** as a pale yellow gum (0.09 g, 93%). $\delta_H(CDCl_3)$ = 8.83 (d, J = 9.1 Hz, 1H, H-10), 8.78 (dq, J = 8.3, 1.0 Hz, 1H, H-8'), 8.28 (d, J = 1.8 Hz, 1H, H-8), 8.26 (d, J = 1.8 Hz, 1H, H-6), 8.25 (s, 1H, H-3), 8.24 (d, J = 9.1 Hz, 1H, H-9), 8.12 (d, J = 9.0 Hz, 1H, H-5), 8.07 (d, J = 9.0 Hz, 1H, H-4), 7.90 (ddt, J = 8.0, 1.3, 0.7 Hz, 1H, H-5'), 7.87 (d, J = 8.4 Hz, 1H, H-4'), 7.68 (ddd, J = 8.3, 6.8, 1.2 Hz, 1H, H-7'), 7.55 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H, H-6'), 7.55 (d, J = 8.4 Hz, 1H, H-3'), 7.04 (dd, J = 7.9, 5.3 Hz, 1H, H-1''), 5.90 (dddd, J = 17.0, 10.2, 7.3, 6.6 Hz, 1H, H-3''), 5.11 (dq, 17.0, 1.5 Hz, 1H, H-

4″a), 5.06 (ddt, J = 10.2, 1.8, 1.1 Hz, 1H, H-4″b), 3.55 (t, J = 7.6 Hz, 2H, H-1′′′′), 3.00

(ddt, J = 14.6, 6.6, 1.2 Hz, 1H, H-2″), 2.94 (dtt, J = 14.6, 7.5, 1.2 Hz, 1H, H-2″), 2.82 (dt.

J = 7.6, 2.6 Hz, 2H, H-2′′′′), 2.22 (s, 3H, H-b″), 2.08 (t, J = 2.6 Hz, 1H, H-4′′′′), 1.60 (s,

9H, H-2′′′) ppm; δ_C(CDCl$_3$) = 170.2 (s, C-a″), 149.5 (d, C-7), 141.5 (s, C-2′), 139.5 (s, C-

2), 133.8 (s, C-8′a), 133.4 (d, C-3″), 132.2 (s, C-10a), 132.1 (s, C-4′a), 131.0 (s, C-3a and

C-8a), 130.8 (s, C-5a), 129.2 (d, C-9), 128.9 (d, C-5′), 128.8 (d, C-5), 128.7 (d, C-4′),

127.4 (d, C-3′), 127.2 (d, C-7′), 127.1 (d, C-4), 126.5 (d, C-8′), 126.0 (d, C-6′), 125.6 (d,

C-10), 123.9 (s, C-10b), 123.13 (d, C-8), 123.09 (d, C-6), 121.8 (d, C-3), 119.7 (s, C-1′),

118.2 (t, C-4″), 115.7 (s, C-1), 96.7 (s, C-b), 95.1 (s, C-a), 83.8 (s, C-3′′′), 74.1 (d, C-1″),

69.3 (d, C-4′′′′), 41.2 (t, C-2″), 35.3 (s, C-1′′′), 34.7 (t, C-1′′′′), 31.9 (q, C-2′′′), 21.3 (q, C-

b″), 20.2 (t, C-2′′′′) ppm; IR ν = 3309 (m), 3079 (w), 3053 (w), 2967 (s), 2188 (w), 2118

(w), 1737 (s), 1648 (w), 1643 (w), 1602 (w), 1590 (w), 1567 (w), 1507 (w), 1479 (w),

1461 (w), 1432 (w), 1417 (w), 1395 (m), 1364 (m), 1342 (m), 1239 (s), 1154 (w), 1026

(m), 994 (w), 925 (m), 887 (m), 639 (m), 604 (w) cm^{-1}; MS (EI) m/z (relative intensity) =

572 (M$^+$, 100), 512 (16), 321 (38), 178 (44), 84 (47), 71 (70), 57 (92); HRMS [M$^+$] calcd

for C$_{42}$H$_{36}$O$_2$ 572.2715, found 572.2720.

5.6. References

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24. As per the findings from the Starý group, this catalyst has been found to achieve [2+2+2] cycloisomerization of other triynes under milder reaction conditions as compared to other cobalt-catalysts.

5.7. Appendix

NMR Spectra for Selected Compounds

27

32

33

37225

NMR spectrum

0.429

1.569

1.597

4836.820
4845.946
4855.823
4865.072

4920.173
4920.674
4929.744

4955.488
4957.300

4973.947
4975.769

11.012
11.010
11.015

5175.225
5183.076
5184.321

ppm scale: 0.43 · 1.58 · 1.60 · 8.10 · 8.15 · 8.20 · 8.25 · 8.30 · 8.35 · 8.40 · 8.45 · 8.50 · 8.55 · 8.60 ppm

388

389

37225

CH₂OH —— SiMe₃

36

Acetone

38314

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

1.01 1.02 0.98 0.99 1.12 1.00 1.06 1.08   1.86   3.04 1.71 8.30

38314

38378

393

6759.741

5356.815
5347.699

5258.060

5177.982
5177.082
5176.001
5175.101

5169.580
5168.680
5167.599
5166.699

4992.362
4989.901
4988.041

4983.120
4980.981
4979.279

4893.236

4751.649
4750.929
4750.209

4743.428
4742.827
4741.987

4732.325
4731.725

4723.623

ppm 8.92 ppm
ppm
ppm
8.63
8.62
8.61 ppm
8.32
8.31
8.30 ppm
ppm
7.92
7.91
7.90
7.89
7.88
7.87 ppm

4615.000
4613.739
4608.218
4606.778
4605.218
4599.876
4598.556

4566.719
4558.347

4546.825
4545.625
4540.104
4538.723
4537.463
4531.882
4530.742

2125.600
2118.219
2110.897

1739.237
1731.748
1724.354

965.049

941.730
936.599

580.604
578.810
577.490

7.68 7.66 7.64 7.62 7.60 7.58 7.56 ppm
3.54 3.52 ppm
2.90 2.88 ppm
1.82 1.60 1.58 1.56 ppm
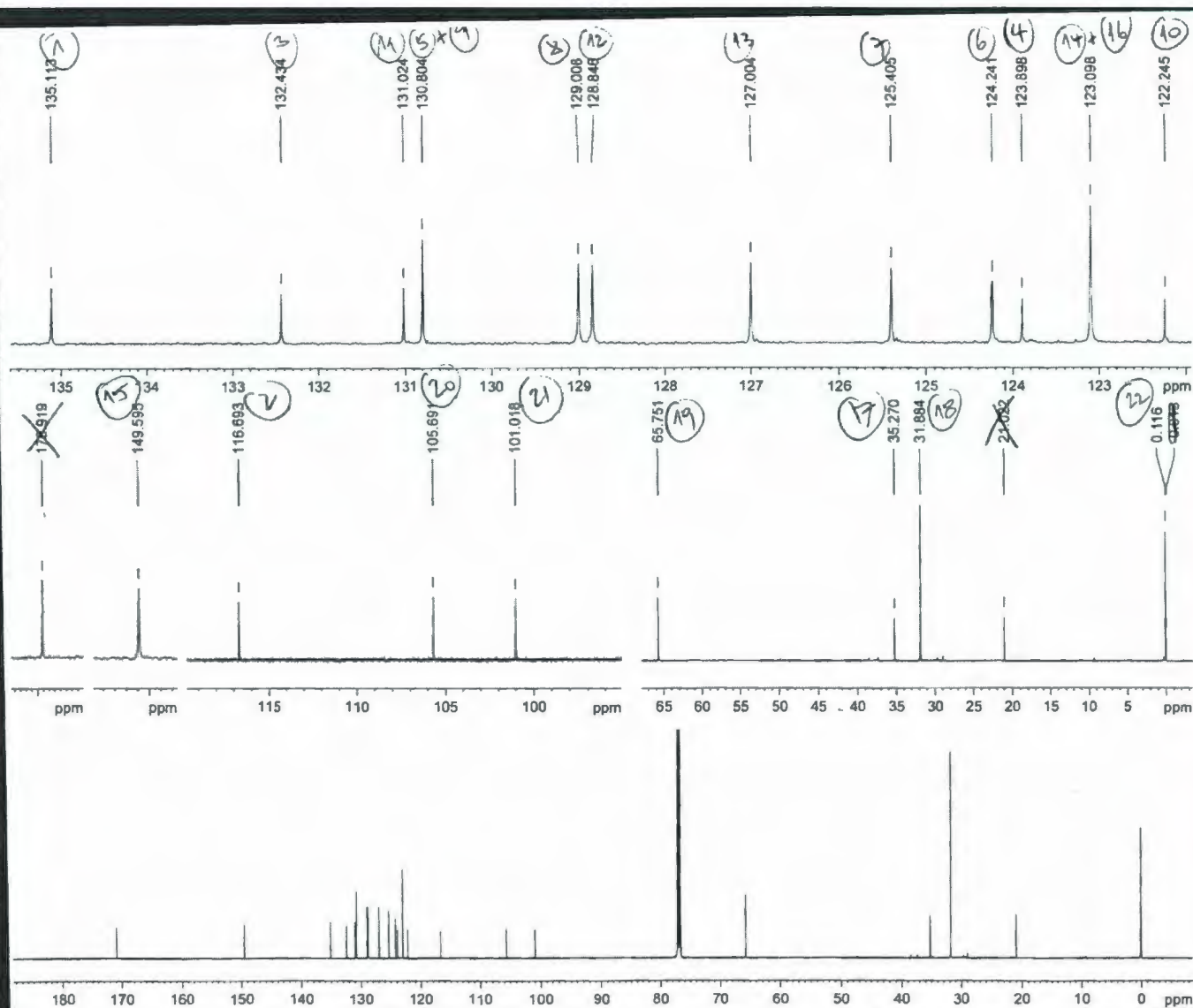0.98 0.97 0.96 0.95 ppm

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in CDCl3, ref=TMS
27.5.2008 DA

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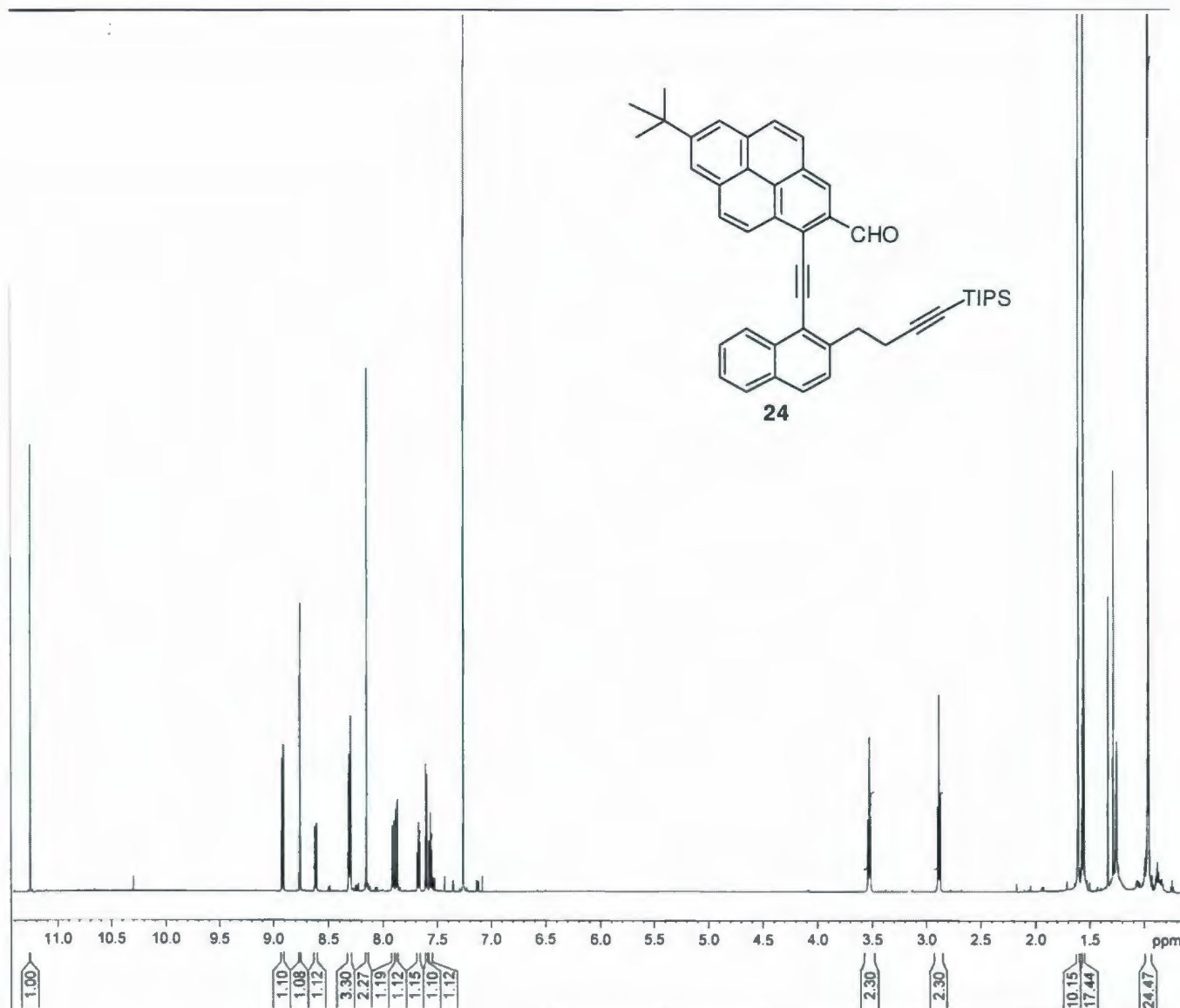F2 - Acquisition Parameters
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NS   2048
DS   0
SWH   29761.904 Hz
FIDRES   0.500032 Hz
AQ   0.9999860 sec
RG   128
DW   16.800 usec
DE   6.50 usec
TE   300.0 K
D1   1.00000000 sec
d11   0.03000000 sec
DELTA   0.89999998 sec
TD0   1
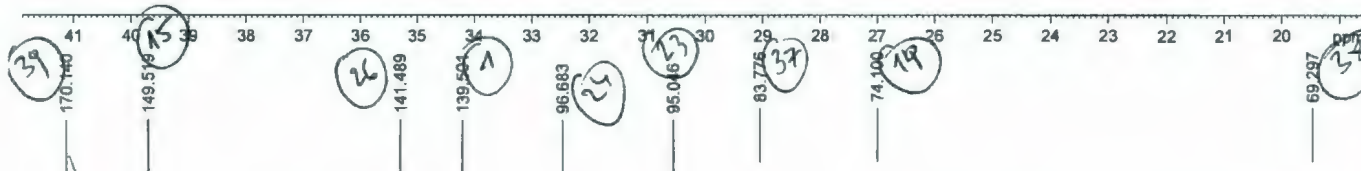
======== CHANNEL f1 ========
NUC1   13C
P1   11.50 usec
PL1   -1.40 dB
SFO1   150.9171448 MHz

======== CHANNEL f2 ========
CPDPRG2   waltz16
NUC2   1H
PCPD2   80.00 usec
PL12   22.00 dB
PL13   25.00 dB
PL2   7.00 dB
SFO2   600.1324005 MHz

F2 - Processing parameters
SI   131072
SF   150.9028127 MHz
WDW   EM
SSB   0
LB   1.00 Hz
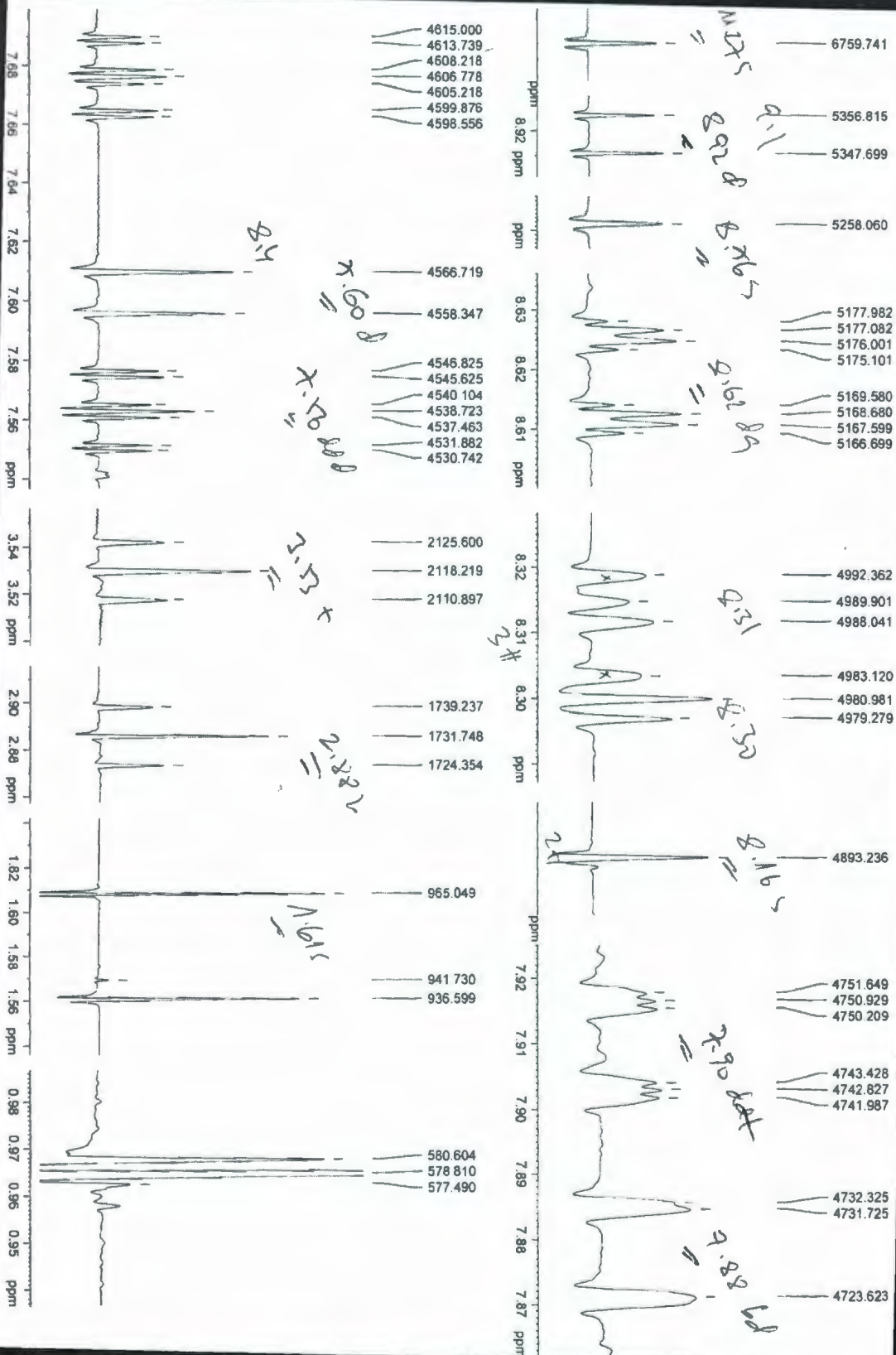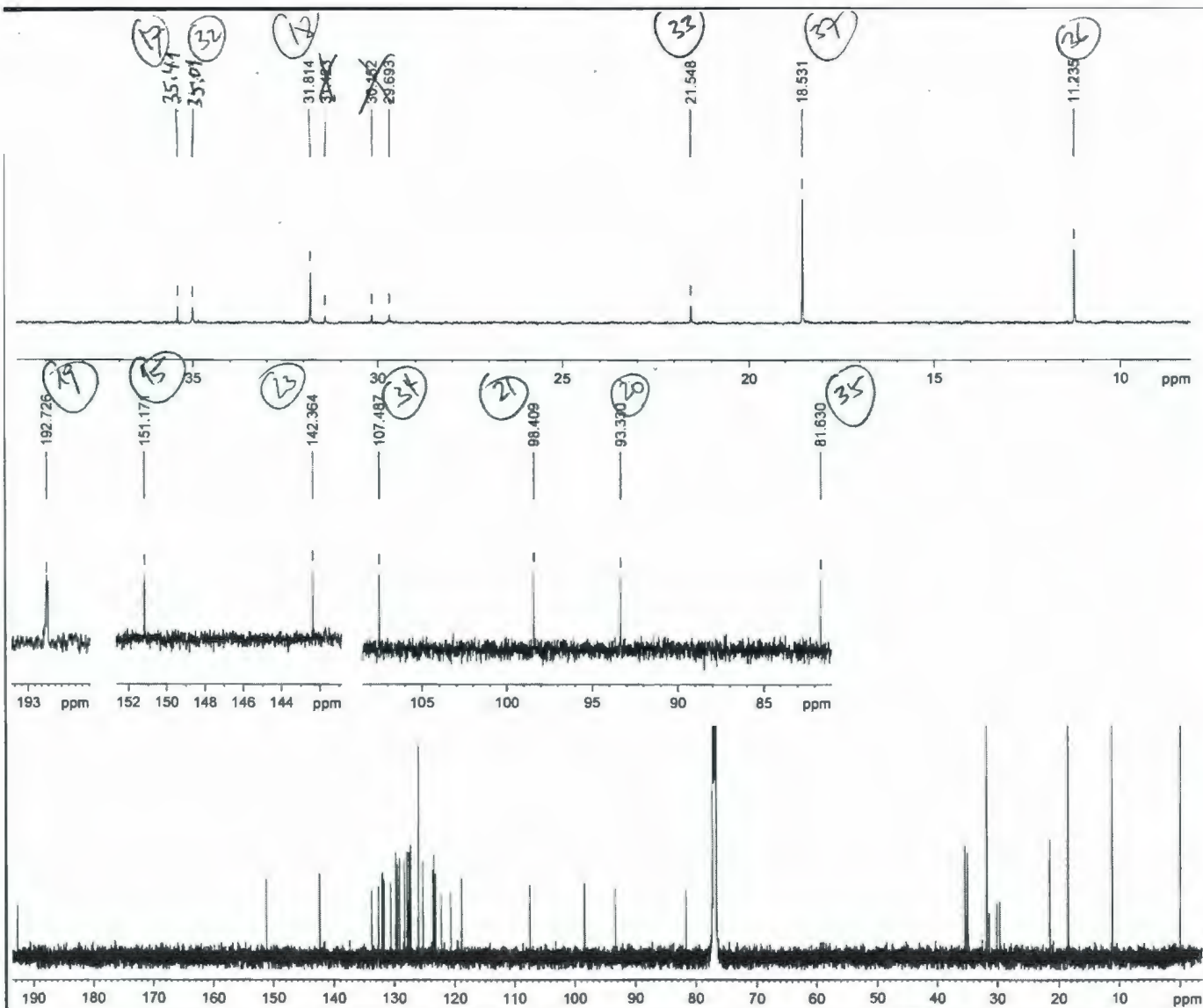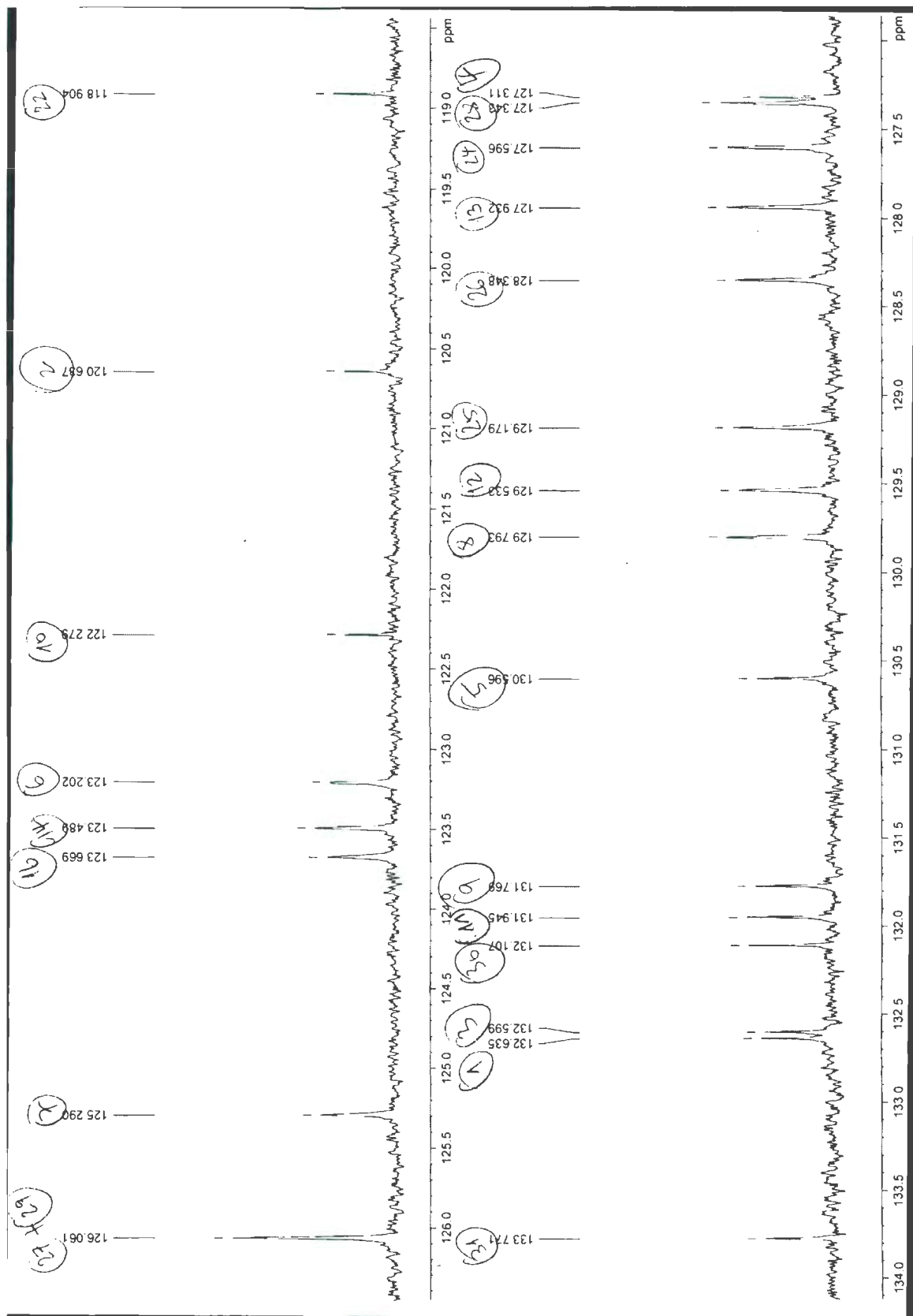GB   0
PC   1.40

38378

395

Peak labels: 35.47, 35.01, 31.814, 30.752, 29.693, 21.548, 18.531, 11.235

192.726, 151.17, 142.364, 107.487, 98.409, 93.330, 81.630

39

38406

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

1.00 1.00   4.09 1.06 1.03 1.03 1.05 1.01 1.04 1.20   0.97   1.01   2.17   2.05   4.02   2.98   9.11   22.60

397

3.03
3.02
3.01
3.00
2.99
2.98
ppm

2.95
2.94
2.93
2.92
2.91
2.90
2.89
2.88
2.87
2.86
ppm

2.218

1.597

1.003
1.000
0.996
0.991

ppm

1.02
1.00
ppm

1817.199
1815.814
1814.445
1812.039
1810.647
1809.263
1807.896
1805.478
1804.094
1802.603
1801.126
1799.739
1797.336
1795.962
1794.576
1793.196
1790.806
1789.423
1788.029

5.93
5.92
5.91
5.90
5.89
5.88
5.87
5.86
ppm

1772.497
1771.311
1770.094
1767.772
1765.129
1763.541
1760.538
1757.805
1757.007
1756.051
1754.781
1753.121
1750.674
1748.074
1743.475
1740.593
1736.069
1733.225
1730.985
1723.535
1716.191

5.12
5.11
5.10
5.09
5.08
5.07
5.06
5.05
ppm

3.58
3.57
3.56
3.55
3.54
3.53
3.52
3.51
ppm

3555.945
3549.439
3548.609
3545.747
3542.067
3539.069
3538.488
3532.289
3531.643
3528.658
3525.004
3522.166
3521.334
3514.789

3075.226
3073.752
3072.067
3070.607
3058.170
3056.668
3054.966
3053.533
3044.171
3043.083
3042.105
3041.284
3040.203
3033.967
3032.870
3031.973
3031.065
3030.005

2150.407
2143.035
2136.973
2135.592
2132.801
2129.580
2125.442
2122.198
2119.415
2118.162
2111.975
2104.763

Left panel (ppm scale 7.68–7.04):

7.68
7.67
7.66 ppm
7.62
7.61 ppm
7.56
7.55
7.54
7.53 ppm
7.14
7.12
7.10
7.08
7.06
7.04 ppm

$\chi.\,4$

Center column:

8.84 ppm
— 4608.084
— 4606.784
— 4601.342
— 4599.887
— 4598.363
— 4592.927
— 4591.620

— 4571.290

— 4562.872

— 4533.956
— 4532.768
— 4527.185
— 4525.940
— 4524.639
— 4519.099
— 4517.892

— 4283.476
— 4280.933
— 4274.857
— 4272.316

— 4250.481

— 4224.707
— 4219.646
— 4216.675
— 4211.675

Center axis labels:
8.27
8.26
8.25
8.24 ppm
8.12
8.10
8.08 ppm
7.90
7.89
7.88
7.87
7.86
7.85
7.84
7.83 ppm

Right column:

— 5302.022
— 5292.953
— 5289.971

— 5265.680
— 5264.807
— 5263.724
— 5262.854
— 5257.270
— 5256.416
— 5255.321
— 5254.429

— 4959.749
— 4957.900
— 4956.365
— 4951.468
— 4949.663
— 4947.246
— 4946.814
— 4942.119

— 4871.618
— 4862.467

— 4842.920
— 4833.642

— 4738.821
— 4738.138
— 4737.421
— 4730.720
— 4730.037
— 4729.333

— 4707.171
— 4706.476

— 4698.309

40

38296

401

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

1.00 1.06   3.39 1.11 1.09 2.03 1.16 1.91   1.18   1.82   2.73   2.12   2.95 2.07   2.54 1.03   6.28

3.56 ppm

2.84 2.83 2.82 2.81 ppm

ppm

2.08 ppm

1.605 ppm

2140.447
2132.842
2125.195

1703.516
1700.912
1696.338
1695.473
1693.686
1692.807
1688.561
1687.882
1685.907
1685.231

1333.31

1250.674
1248.031
1245.386

961.583

38296

7.91 7.90 7.89 7.88 7.87 ppm

8.28 8.26 8.24 8.22 8.20 8.18 8.16 8.14 8.12 8.10 8.08 ppm

8.84 8.83 8.82 8.81 8.80 8.79 8.78 8.77 ppm

4746.229
4745.516
4744.796
4738.096
4737.390
4736.686
4729.575
4721.368

4970.502
4968.690
4956.005
4953.641
4948.543
4944.072

4875.829
4866.777
4846.912
4837.896

5304.922
5295.837
5282.967
5272.151
5271.263
5270.194
5269.301
5263.736
5262.869
5261.802
5260.881

7.69 7.68 7.67 ppm
7.57 7.56 7.55 ppm
7.05 7.04 7.03 ppm
5.94 5.92 5.90 5.88 ppm
5.12 5.10 5.08 5.06 ppm

4615.774
4614.471
4609.032
4607.573
4606.045
4600.612
4599.304

4541.677
4540.481
4536.708
4534.927
4533.635
4532.352
4528.297
4526.787
4525.606

4233.690
4228.502
4225.854
4220.598

3561.269
3554.707
3553.963
3551.073
3547.396
3544.329
3537.017
3534.026
3530.336
3527.466
3526.705
3520.117

3076.712
3075.227
3073.545
3072.067
3059.654
3058.143
3056.446
3054.990
3044.593
3043.473
3042.504
3041.680
3040.588
3034.377
3033.264
3032.359
3031.461
3030.385

38296

405