Chapter 4

Synthesis and Photochemical Studies of a Few 2-Aryl-2-hydroxy-1-oxacyclopenta[*l*]phenanthren-3-ones

4.1 Abstract

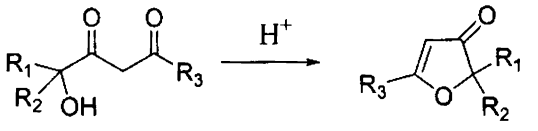
3(2H)-Furanones are valuable synthetic intermediates and key structural subunits of a variety of natural products. This chapter presents our efforts on the development of a new and efficient method for the synthesis of few 2-aryl-2-hydroxy-1-oxacyclopenta[l]phenanthren-3-ones. The protocol developed by us employs readily available phenanthrenequinone and various para substituted acetophenones as starting materials and provides easy access. Our endeavours on the photolysis of above mentioned compounds is also illustrated here. Under the influence of UV radiation these compounds were found to be stable but underwent extensive decomposition to intractable mixture in presence of a tertiary amine.

4.2 Introduction

The 3(2*H*)-furanone ring system is found in a wide variety of natural products including many flavor compounds[1-2] and insect pheromones. Compounds incorporating this functionality or their derivatives have been shown to be biologically active and some display fungicidal, herbicidal, antibiotic, antihelminthic and antitumor activity.[3-8] Natural antitumor agents for example, jatrophone, eremantholides, geiparvarin, chinolone, ciliarin all belong to the group of 3(2*H*)-furanones.[9-12] The potent antitumor properties of many 3(2*H*)-furanones have been associated with their ability to act as Michael acceptors.[13] Apart from the unusual range of biological activity, their

use as reactive intermediates in organic synthesis[14-17] also lent importance to the synthesis of these furanones.

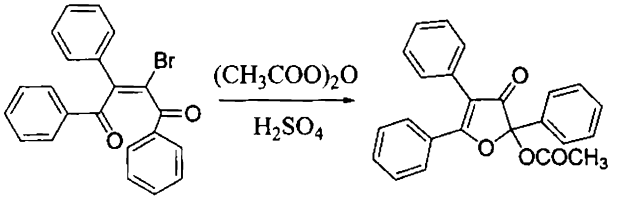
Synthetic approaches to the 3(2*H*)-furanone ring system which vary in their degree of flexibility have appeared in the literature.[18,19] One of the general approaches to the synthesis of these compounds involves the acid catalysed cyclisation–dehydration process of an appropriately substituted α-hydroxy-1,3-diketone (**1**) as in Scheme 1.[21,22,25,26]



1 **2**

Scheme 1

3(2*H*)-Furanones can be easily synthesised from the *cis* isomer of dibenzoylalkenes. *E*-bromodibenzoylstyrenes on addition-cyclisation reaction in presence of acidic reagents yield the corresponding 3(2*H*)-furanones (Scheme 2).[27]

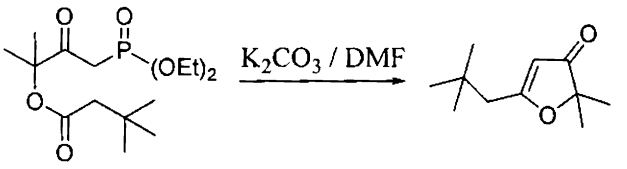


3 **4**

Scheme 2

Sampson *et al.* have utilized a Wadsworth-Emmons type condensation reaction for the key ring formation. When treated with potassium carbonate,

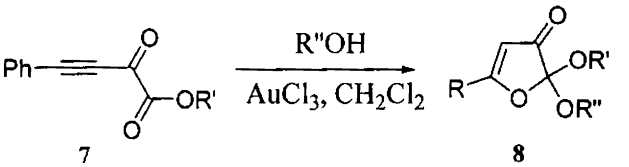
γ-(acyloxy)-β-ketophosphonates **5** undergo an intramolecular condensation to afford 3(2*H*)-furanones.[28]



5 **6**

Scheme 3

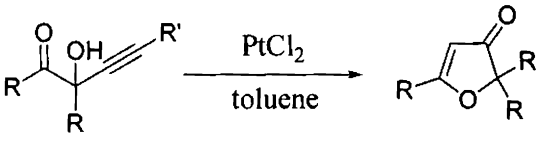
Gold catalysed cyclisations of 2-oxo-3-butynoic esters **7** or disubstituted 1,2-diones with a variety of nucleophiles offer a straightforward route to substituted 3(2*H*)-furanones **8** under mild conditions.[29]



7 **8**

Scheme 4

A novel approach to 3(2*H*)-furanones combines a transition metal catalysed activation of alkynes with a heterocyclisation and subsequent 1,2 alkyl shift.[30]



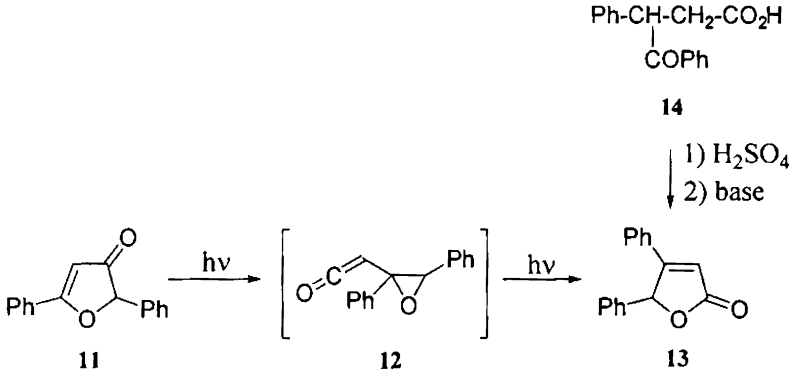
9 **10**

Scheme 5

Although a number of syntheses of 3(2*H*)-furanones were known they were in many cases limited to specific substitution patterns. The development

of alternative strategies for the preparation of these heterocyclics is therefore of considerable importance and continues to be a challenge. In this chapter we present a very facile and efficient procedure which enables the conversion of the easily accessible starting materials into 3(2*H*)-furanones. The protocol developed by as involves a two step process consisting of Claisen-Schmidt condensation of phenanthrenequinone with various para substituted acetophenones followed by acid treatment. Aryl ketones of our choice were acetophenone, 4-methylacetophenone, 4-methoxyacetophenone, 4-chloro-acetophenone and 4-phenylacetophenone.

Eventhough the synthesis and reactions of 3(2*H*)-furanones have attracted considerable attention, the intramolecular photochemistry of these compounds, but for a few preliminary examinations, remained largely unexplored. Padwa and coworkers[31] found that irradiation of 2,5-diphenyl-3(2*H*)-furanone **(11)** in benzene under argon atmosphere yielded 4,5-diphenyl-2(5*H*)-furanone **(13)**.

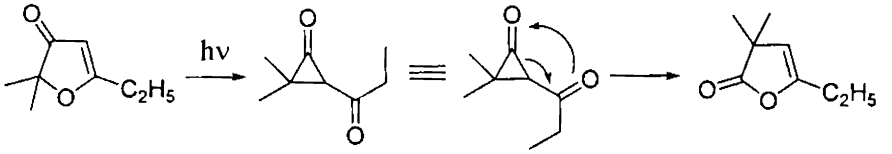


11 12 13

Scheme 6

Agosta and coworkers[32] reported that on irradiation, alkyl-substituted 3(2*H*)-furanone **15** rearranged to the corresponding 2(3*H*)-furanone **17**. The

mechanism involves the formal cyclopentene-vinylcyclopropane rearrangement of **15** to **16** followed by the reverse process with involvement of the other cyclopropane center to yield **17.**



15 **16** **17**

Scheme 7

Highly-crowded 2,2-dimethyl-4,5-di-*tert*-butyl-3(2*H*)-furanone on the other hand gave the decarbonylated product as major and 2,2-dimethyl-4-*tert*-butyl-3(2*H*)-furanone as minor product on irradiation in benzene. The mechanism involves the rearrangement of the furanone to an acylcyclopropanone followed by decarbonylation to yield the product.

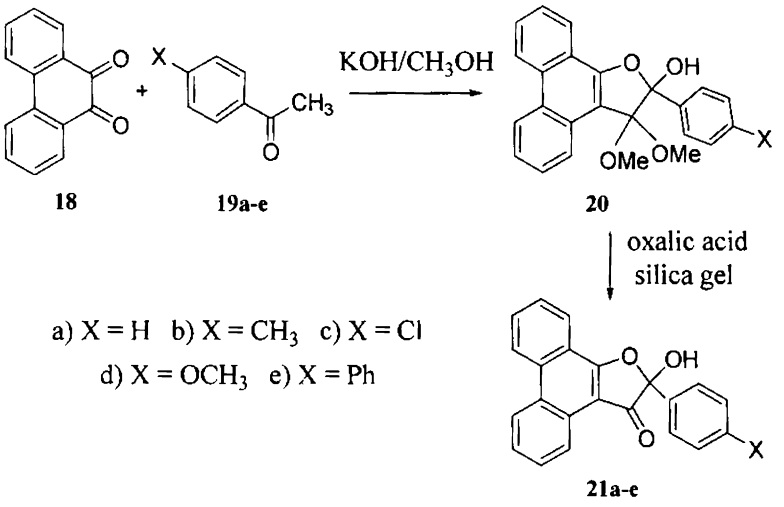
Based on these observations we expected that our systems, 2-aryl-2-hydroxy-1-oxacyclopenta[*l*]phenanthren-3-ones would also undergo analogous rearrangements. Our endeavours on the synthesis and photochemistry of these compounds are depicted in this chapter.

4.3 Results and Discussion

4.3.1 Synthesis of 2-Aryl-2-hydroxy-1-oxacyclopenta[*l*]phenanthren-3-ones

The condensation of phenanthrenequinone **(18)** with acetophenones **19a-e** in the presence of potassium hydroxide in methanol gave 3,3-dimethoxy-2-aryl-2,3-dihydro-1-oxacyclopenta[*l*]phenanthren-2-ols **20a-e** in 25-40% yields.[33] Close examination of the structural features of these

compounds reveals that it may be regarded as the dimethylketals of 2-aryl-2-hydroxy-1-oxacyclopenta[*l*]phenanthren-3-ones **21**. So we attempted the conversion of furanol derivatives to corresponding 3(2*H*)-furanones. Furanol derivatives **20a-e** was dissolved in dichloromethane and oxalic acid adsorbed on silica gel was added. After stirring at room temperature for 12 hours, the product formed was separated by column chromatography and recrystallised from a mixture (2:1) of dichloromethane and hexane to give 2-aryl-2-hydroxy-1-oxacyclopenta[*l*]phenanthren-3-ones **21a-e** as white solid.



18 **19a-e** **20** **21a-e**

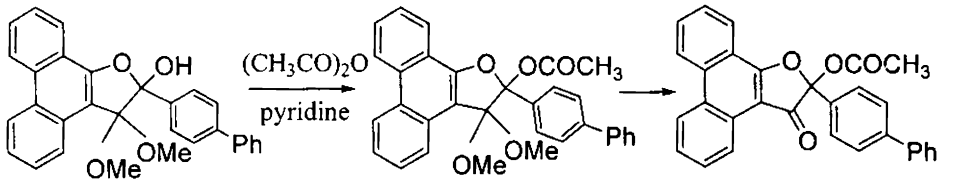
Scheme 8

The structure of these derivatives was arrived at on the basis of spectral and analytical data. 2-Hydroxy-2-phenyl-1-oxacyclopenta[*l*]phenanthren-3-one **(21a)** was obtained in 65% yield and showed strong IR absorptions at 3419 and 1688 cm^{-1} indicating the presence of a hydroxyl and carbonyl group respectively in the molecule. ^1H NMR spectrum of this compound showed a singlet at δ 2.24 corresponding to the hydroxyl proton, and multiplet between

δ 7.20-8.95 corresponding to thirteen aromatic protons. The ^{13}C NMR spectrum showed the carbonyl carbon at δ 197.12. Similarly, 2-hydroxy-2-(*p*-tolyl)-1-oxacyclopenta[*l*]phenanthren-3-one **(21b)** obtained in 67% yield showed strong IR absorptions at 3410 and 1678 cm^{-1} due to hydroxyl and carbonyl groups in the compound. In ^{1}H NMR spectrum the compound showed a singlet at δ 2.29 and δ 2.50 corresponding to the hydroxyl proton and three protons of the methyl group respectively. A multiplet at δ 7.19-8.95 corresponds to twelve aromatic protons. The ^{13}C NMR spectrum showed the carbonyl carbon at δ 196.12. 2-(4-Chlorophenyl)-2-hydroxy-1-oxa-cyclopenta[*l*]phenanthren-3-one **(21c)** obtained in 66% yield shows strong IR absorptions at 3424 and 1672 cm^{-1} due to hydroxyl and carbonyl groups. In the ^{1}H NMR spectrum the compound showed a singlet at δ 2.46 due to hydroxyl proton and multiplet at δ 7.42-8.92 corresponding to twelve aromatic protons. The ^{13}C NMR spectrum showed the carbonyl carbon at δ 196.73. 2-Hydroxy-2-(4-methoxyphenyl)-1-oxacyclopenta[*l*]phenanthren-3-one **(21d)** obtained in 67% yield showed strong IR absorptions at 3415 and 1679 cm^{-1} respectively due to hydroxyl and carbonyl groups. The compound showed a singlet at δ 2.50 corresponding to the proton of hydroxyl group, a singlet at δ 3.72 due to three protons of the methoxy group, and a multiplet at δ 6.96-8.94 corresponding to twelve aromatic protons. The ^{13}C NMR spectrum showed the carbonyl carbon at δ 197.43. 2-Biphenyl-4-yl-2-hydroxy-1-oxa-cyclopenta[*l*]phenanthren-3-one **(21e)** obtained in 68% yield showed strong IR absorptions at 3418 and 1677 cm^{-1} due to hydroxyl and carbonyl groups. The compound showed a singlet at δ 2.38 due to one hydroxyl proton and multiplet between δ 7.35-8.98 corresponding to aromatic protons in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum showed the carbonyl carbon at δ 197.02.

The structures were further confirmed by elemental analysis, which gave acceptable data. The absorption spectra of all these 3(2*H*)-furanones are dominated by the absorption due to the phenanthrene component present in them.

Similarly acetylation of compound **20** using acetic anhydride in pyridine was done on a representative sample **20e.** The structure of the acetoxy furanone derivative **23e** was arrived at on the basis of spectral and analytical data. It seems likely that the initial acetylation product **22** formed underwent hydrolysis during aqueous workup of the reaction mixture. 2-Biphenyl-4-yl-3-oxo-2,3-dihydro-1-oxacyclopenta[*l*]phenanthren-2-yl acetate **(23e),** which was obtained in 63% yield showed prominent peaks at 1770 and 1688 cm^{-1} in the IR spectra indicating the presence of two carbonyl groups in the compound. In the ^{1}H NMR spectrum, one singlet was observed at δ 2.29 due to the presence of three protons of acetoxy group and multiplet at δ 7.35-8.97 corresponding to twelve aromatic protons in the compound. The ^{13}C NMR spectrum showed peaks at δ 172.65 and 197.40 due to carbonyl carbons. As in the case of hydroxyfuranones **21**, the absorption spectrum of **23e** was also dominated by the phenanthrene component.



20 e 22 23 e

Scheme 9

4.3.2 Photochemical Transformations

Based on the reports that 3(2*H*)-furanones undergo interesting photochemical transformations, for example rearrangement to 2(5*H*)-furanones, we carried out irradiation experiments on a few representative examples. A solution of 2-hydroxy-2-phenyl-1-oxacyclopenta[*l*]phenanthren-3-one **(21a)** (0.70 mmol in 130 mL) in acetone purged with nitrogen was irradiated (RPR, 350 nm). Even after 18 hours no new products were observed and starting compound recovered unchanged.

The compound was found to be stable under the irradiation condition employed by us. We conclude that the excitation energy in **21** is concentrated in the phenanthrene component. Consequently, **21**, unlike other simple 3(2*H*)-furanones examined by Padwa and Agosta are less likely to undergo photochemical transformations characteristic of the 3(2*H*)-furanone component. So, we explored the possibility of electron transfer mediated phototransformations with a few representative examples. We selected simple tertiary amines as the electron donors to 3(2*H*)-furanones. Photolysis of **21** was carried out in the presence of a tertiary amine, *N*-methylpyrrolidene to examine their electron transfer mediated phototransformation. But the compound underwent extensive decomposition to yield an intractable mixture under the condition applied by us. Since the acetoxy derivative **23e** underwent slow decomposition in solution, we did not examine its photochemistry.

4.4 Conclusion

We have successfully synthesised few 2-aryl-2-hydroxy-1-oxa-cyclopenta[*l*]phenanthren-3-ones from 3,3-dimethoxy-2-aryl-2,3-dihydro-1-oxacyclopenta[*l*]phenanthren-2-ol precursors using a facile and efficient

synthetic strategy. These furanone derivatives have immense potential for further investigations. The photolysis of these compounds resulted in extensive decomposition leading to intractable mixtures in presence of tertiary amine, but are stable towards UV light on direct irradiation in acetone.

4.5. Experimental

4.5.1. General Procedures

All melting points are uncorrected and were determined on a Neolab melting point apparatus. All reactions and chromatographic separations were monitored by thin layer chromatography (TLC). Glass plates coated with dried and activated silica gel or aluminium sheets coated with silica gel (Merck) were used for thin layer chromatography. Visualization was achieved by exposure to iodine vapours or UV radiation. Column chromatography was carried out with slurry-packed silica gel (Qualigens, 60-120 mesh). Absorption spectra were recorded using Shimadzu 160A spectrometer and infra red spectra were recorded using ABB Bomem (MB Series) FT-IR spectrometer. All steady state irradiations were carried out using Rayonet Photochemical Reactor (RPR). Solvents for photolysis were purified and distilled before use. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively on a Bruker 300 FT-NMR spectrometer with tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane. Elemental analysis was performed using Elementar Systeme (Vario ELIII) at STIC, Kochi.

4.5.2. Starting Materials: Phenanthrenequinone and acetophenones were purchased from Sigma Aldrich and were used as obtained. 3,3-Dimethoxy-2-

aryl-2,3-dihydro-1-oxacyclopenta[*l*]phenanthren-2-ols were synthesised using a known procedure.[33]

4.5.3. Synthesis of 2-Aryl-2-hydroxy-1-oxacyclopenta[*l*]phenanthren-3-ones 21a-e.

4.5.3.1. Synthesis of 2-Hydroxy-2-phenyl-1-oxacyclopenta[*l*]phenanthren-3-one (21a)

A sample of **20a** (5.0 g, 15 mmol) was dissolved in dichloromethane and oxalic acid (5.4 g) adsorbed on silica gel was added. The mixture was stirred at room temperature for 12 h. The progress of the reaction was monitered by using TLC. The product formed was separated by column chromatography and recrystallised from a mixture (2:1) of dichloromethane and hexane gave **21a** as white solid.

Compound 21a (65%); mp 174-176 ^{0}C; IR ν_{max} (KBr) 3419 cm^{-1} (OH), 1688 cm^{-1}(C=O), 1624 cm^{-1} ; UV λ_{max} (CH_3CN) 208 (ε 23,300), 225 (ε 20,000), 246 (ε 29,900), 257 (ε 22,000), 275 (ε 10,500), 304 (ε 5,000), 339 (ε 2,400), 355 nm (ε 2,000); ^{1}H NMR ($CDCl_3$) δ 2.24 (1H, s, OH), 7.20-8.95 (m, 13H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 106.75, 120.72, 122.62, 123.26, 123.90, 124.39, 126.17, 126.38, 126.47, 126.61, 126.80, 126.95, 127.79, 128.19, 129.02, 129.13, 132.81, 135.58, 139.53, 141.17, 172.64, 197.12.; Anal. Calcd for $C_{22}H_{14}O_3$: C, 80.96; H, 4.32. Found: C, 79.89; H, 4.54.

4.5.3.2. Synthesis of 2-Hydroxy-2-(*p*-tolyl)-1-oxacyclopenta[*l*]phenanthren-3-one (21b)

A sample of **20b** (5.0 g, 14 mmol) was dissolved in dichloromethane and oxalic acid (5.0 g) adsorbed on silica gel was added. The mixture was stirred

at room temperature for 12 h. The progress of the reaction was monitered by using TLC. The product formed was separated by column chromatography and recrystallised from a mixture (2:1) of dichloromethane and hexane gave **21b** as white solid.

Compound 21b (67%); mp 180-182 ^{0}C; IR ν_{max} (KBr) 3410 cm^{-1} (OH), 1678 cm^{-1}(C=O), 1620 cm^{-1} ; UV λ_{max} (CH_3CN) 220 (ε 19,555), 239 (ε 29,040), 256 (ε 21,914), 275 (ε 10,500), 300 (ε 4,930), 340 (ε 2,410), 351 (ε 2,480), 361 nm (ε 2,820); ^{1}H NMR ($CDCl_3$) δ 2.29 (1H, s, OH), 2.50 (s, 3H, methyl protons), 7.19-8.95 (m, 12H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 25.32, 106.19, 121.12, 122.42, 122.26, 123.10, 124.39, 126.37, 126.38, 126.47, 126.60, 126.63, 128.95, 129.11, 129.19, 129.22, 129.53, 129.80, 132.42, 139.50, 140.17, 166.14, 196.12.; Anal. Calcd for $C_{23}H_{16}O_3$: C, 81.16.; H, 4.72. Found: C, 80.20; H, 4.69.

4.5.3.3. Synthesis of 2-(4-Chlorophenyl)-2-hydroxy-1-oxacyclopenta[*l*] phenanthren-3-one (21c)

A sample of **20c** (5.0 g, 13 mmol) was dissolved in dichloromethane and oxalic acid (4.7 g) adsorbed on silica gel was added. The mixture was stirred at room temperature for 12 h. The progress of the reaction was monitered by using TLC. The product formed was separated by column chromatography and recrystallised from a mixture (2:1) of dichloromethane and hexane gave **21c** as white solid.

Compound 21c (66%); mp 214-216 ^{0}C; IR ν_{max} (KBr) 3424 cm^{-1} (OH), 1672 cm^{-1}(C=O), 1626 cm^{-1} ; UV λ_{max} (CH_3CN) 234 (ε 26,215), 246 (ε 24,900), 259 (ε 11,900), 295 (ε 2,890), 302 (ε 2,540), 347 (ε 1569), 354 nm (ε 1,580); ^{1}H NMR ($CDCl_3$) δ 2.46 (1H, s, OH), 7.42-8.92 (m, 12H, aromatic protons);

^{13}C NMR ($CDCl_3$) δ 105.46, 106.63, 120.61, 122.61, 123.22, 123.82, 124.30, 126.16, 126.47, 127.73, 128.10, 128.63, 129.07, 129.44, 131.02, 131.72, 132.75, 134.11, 135.39, 135.56, 139.61, 172.59, 196.73 Anal. Calcd for $C_{22}H_{13}ClO_3$: C, 73.26.; H, 3.62. Found: C, 73.19; H, 3.64.

4.5.3.4. Synthesis of 2-Hydroxy-2-(4-methoxyphenyl)-1-oxacyclopenta[*l*]-phenanthren-3-one (21d)

A sample of **20d** (5.0 g, 14 mmol) was dissolved in dichloromethane and oxalic acid (5.0 g) adsorbed on silica gel was added. The mixture was stirred at room temperature for 12 h. The progress of the reaction was monitered by using TLC. The product formed was separated by column chromatography and recrystallised from a mixture (2:1) of dichloromethane and hexane gave **21d** as white solid.

Compound 21d (67%); mp 132-134 ^0C; IR ν_{max} (KBr) 3415 cm^{-1} (OH), 1679 cm^{-1}(C=O), 1628 cm^{-1} ; UV λ_{max} (CH_3CN) 248 (ε 16,740), 251 (ε 14,980), 256 (ε 11,960), 297 (ε 2,970), 300 (ε 2900), 347 (ε 1,569), 351 (ε 1,380), 356 nm (ε 1690); ^1H NMR ($CDCl_3$) δ 2.50 (1H, s, OH), 3.72 (s, 3H, methoxy protons), 6.96-8.94 (m,12H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 55.27, 106.29, 106.76, 113.99, 120.81, 122.66, 123.26, 123.88, 124.36, 126.12, 126.44, 126.73, 127.26, 127.79, 128.16, 128.44, 129.12, 132.79, 135.55, 160.08, 161.11, 172.50, 197.43; Anal. Calcd for $C_{23}H_{16}O_4$: C, 77.50.; H, 4.51. Found: C, 77.57; H, 4.54.

4.5.3.5. Synthesis of 2-Biphenyl-4-yl-2-hydroxy-1-oxacyclopenta[*l*]phen-anthren-3-one (21e)

A sample of **20e** (5.0 g, 12 mmol) was dissolved in dichloromethane and oxalic acid (4.3 g) adsorbed on silica gel was added. The mixture was stirred

at room temperature for 12 h. The progress of the reaction was monitered by using TLC. The product formed was separated by column chromatography and recrystallised from a mixture (2:1) of dichloromethane and hexane gave **21e** as white solid.

Compound 21e (68%); mp 205-207 ^{0}C; IR ν_{max} (KBr) 3418 cm^{-1} (OH), 1677 cm^{-1}(C=O), 1629 cm^{-1} ; UV λ_{max} (CH_3CN) 251 (ε 14,980), 253 (ε 13,290), 304 (ε 1,879), 350 (ε 1569), 351 nm (ε 1,380); ^{1}H NMR ($CDCl_3$) δ 2.38 (1H, s, OH), 7.35-8.98 (m, 17H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 106.14, 106.76, 120.83, 122.65, 123.35, 123.91, 124.46, 125.71, 126.51, 126.73, 126.76, 128.26, 128.64, 129.21, 129.69, 130.95, 132.87, 133.58, 135.68, 138.91, 160.17, 172.60, 197.02; Anal. Calcd for $C_{28}H_{18}O_3$: C, 83.53.; H, 4.52. Found: C, 83.41; H, 4.54.

4.5.4. Synthesis of 2-Biphenyl-4-yl-3-oxa-2,3-dihydro-1-oxacyclopenta[*l*]-phenanthren-2-yl acetate (23e)

A sample of **20e** (5.0 g, 12 mmol) was dissolved in dichloromethane and pyridine was added. Acetic anhydride was added dropwise to the reaction mixture over a period of 30 minutes and then refluxed for 2 h. The progress of the reaction was monitered by using TLC. After workup the product formed was separated by column chromatography and was then recrystallised from a mixture (2:1) of dichloromethane and hexane to give **23e** as white powder.

Compound 23e (63%); mp 182-184 ^{0}C; IR ν_{max} (KBr) 1770, 1688 cm^{-1}(C=O), 1624 cm^{-1} ; UV λ_{max} (CH_3CN) 205 (ε 25,300), 246 (ε 23,900), 257 (ε 18,000), 304 (ε 8,000), 355 nm (ε 2,000); ^{1}H NMR ($CDCl_3$) δ 2.29 (3H, s, acetoxy), 7.35-8.97 (m, 12H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 20.88, 106.34, 106.78, 1.8,122.69, 123.32, 123.97, 124.45, 125.76, 126.22, 126.51,

126.73, 128.26, 128.60, 129.21, 129.61, 130.09, 132.84, 133.58, 135.61, 138.90, 161.11, 172.65, 197.40.; Anal. Calcd for $C_{30}H_{20}O_4$: C, 81.07; H, 4.54. Found: C, 81.30; H, 4.14.

4.5.4 Irradiation of 2-Hydroxy-2-phenyl-1-oxacyclopenta[*l*]phenanthren-3-one (21a) in acetone

In a typical irradiation experiment, a solution of **21a** in acetone (0.70 mmol in 130 mL) was purged with nitrogen for 20 min and then irradiated (RPR, 350 nm) for 18 h. The reaction was monitored by TLC. Solvent was removed and the residue was charged to a column of silica gel. The starting compound **21a** was recovered unchanged. Similar results were obtained with **21b-e**.

4.5.6 Irradiation of 2-Hydroxy-2-phenyl-1-oxacyclopenta[*l*]phenanthren-3-one (21a) in acetone in presence of *N*-Methylpyrrolidine.

In a typical irradiation experiment, a solution of **(21a)** in acetone (0.70 mmol in 130 mL) containing *N*-methylpyrrolidine (542 mg, 6.37 mmol) was purged with nitrogen for 20 min and then irradiated (RPR, 350 nm) for 6 h. The reaction was monitored by TLC. Solvent was removed and the residue was charged to a column of silica gel. An intractable mixture resulted.

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