JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b00786 • Publication Date (Web): 06 May 2019

Just Accepted

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

The photo-Fries rearrangement of some 3-acylestrone in homogeneous media. Preparative and mechanistic studies.

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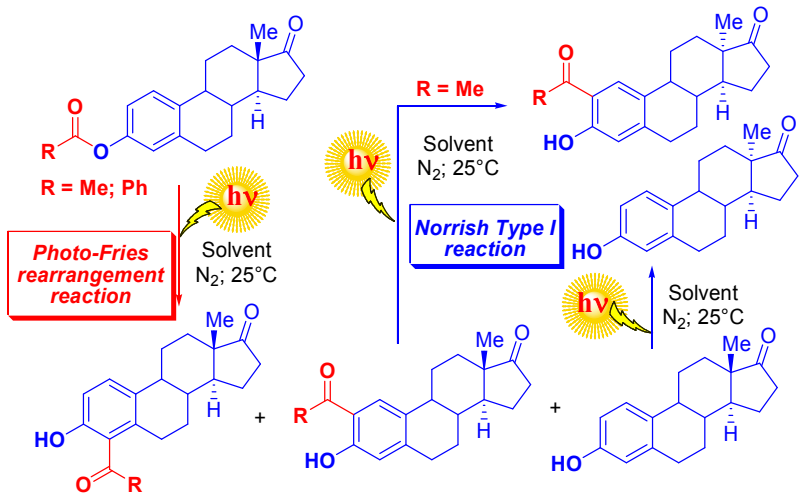


Abstract. Irradiation of a series of 3-acylestrones under nitrogen atmosphere in cyclohexane, MeCN and MeOH was investigated under steady-state conditions. The molecules underwent the photo-Fries rearrangement, with concomitant homolytic fragmentation of the ester group and [1;3]-acyl migration. This pathway afforded the *ortho*-acyl estrone derivatives, the main photoproducts

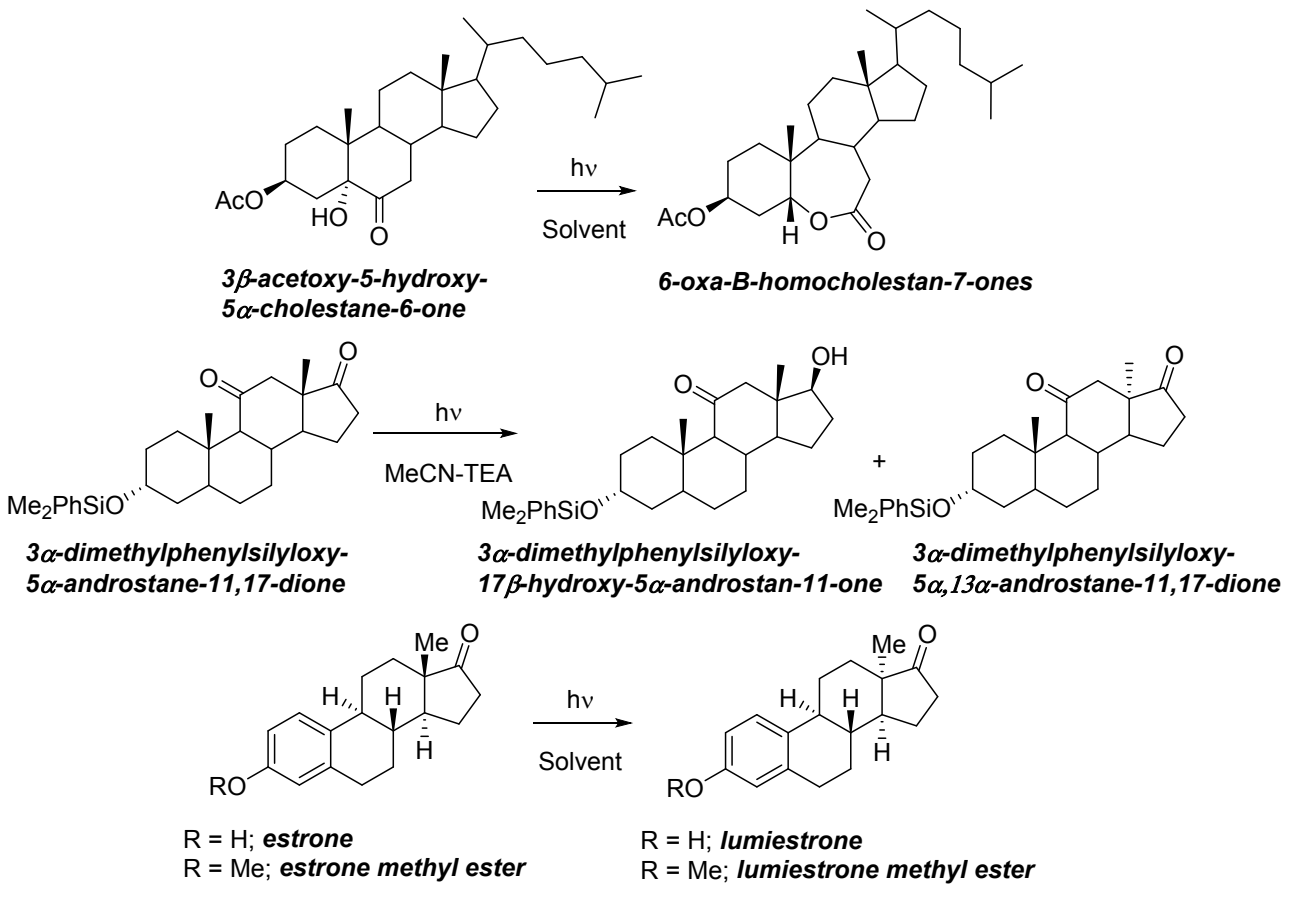
together with estrone. During the irradiation of 3-benzoyl estrone, epimerization of estrone through the Norrish Type I reaction occurred, providing lumiestrone as the photoproduct. This photoreaction involves the fragmentation of the C-α at the carbonyl group (C-17) of the steroid. On the other hand, epimerization of *ortho*-regioisomer 2-acetyl estrone occurred during the irradiation of 3-acetyl estrone. Photosensitization with acetone and chemical quenching with *N,N,N,N*-tetramethyldiazetinedioxide of the photo-Fries reaction confirmed that the photoreaction took place from the singlet excited state while the Norrish Type I reaction proceeds efficiently from the triplet excited state. Solvent effects, as well as the nature of the acyl group on the photoreactions, were also studied.

Introduction.

Steroidal sex hormones such as estrone and estradiol have attracted the attention of organic chemists because these tetracycles possess significant physiological activity and because they represent a clear challenge for total synthesis.[1] These estrogens play a role in many biological processes, consequently they are used as a scaffold for numerous steroidal derivatives. Not surprisingly, compounds based on these moieties are used as drugs for the treatment of a variety of medical conditions.[2] Thus, improved methods for preparing already known derivatives and the synthesis of new estrogen scaffolds is of considerable importance. For example, modification of estrone at position 6, 16, or 17 positions provided novel potent inhibitors of 17β-hydroxysteroids dehydrogenase type 1 (17β-HSD).[3] This enzyme is expressed in all classical steroidogenic tissues and almost all peripheral tissues, including the skin and breast. Moreover, it is highly expressed in malignant breast cells.[3]

The photochemistry of steroids was thoroughly studied throughout the years,and the photochemical work on these compounds included a considerable amount of photochemical reactions in solution such as photorearrangement, photoaddition, photoreduction and photooxidation reactions.[4] Also, photochemical approaches have been successfully applied toward the synthesis of a variety of

natural products, i.e. α-cedrene, ingenol, estrone and ginkgolide B.[5]Preparative and mechanistic studies on the photolysis of steroids, also considering the stereospecificity of the photoreaction have been carried out.[6] For example, photolysis of 5-hydroxy-5α- and 5β-cholestan-6-one and their 3β-acetoxy and 3β-benzyloxy derivatives provided the corresponding lactones, 6-oxa-B-homocholestan-7-ones with retention of the configuration at C-5 (see Scheme 1).[6b]Likewise, Morrison and co-workers have shown that 3α-(dimethylphenylsilyloxy)-5a-androstane-6,17-dione and its 3β isomer gave photoreduction and C-α fragmentation of carbonyl group at C-17 of the steroids (see Scheme 1). This behavior was attributed to the antenna-photosensitization through triplet and singlet energy transfer from the arylsilyloxy group to the carbonyl groups.[6g]



Scheme 1. Photochemistry of some steroidal derivatives.

Estrone and its derivatives were also subjected to direct irradiation in solution and neat C-α fragmentation followed by epimerization of methyl group at C-13 through a Norrish Type I reaction occurred (see Scheme 1). Irradiation of estrone 3-methyl ether provided lumiestrone 3-methyl ether as the main photoproduct in 53 % yield along with seco-steroids as byproducts when anhydrous THF was used as solvent.[7] Estrone was also irradiated with UV-B (280 – 320 nm) under aerobic conditions in acetonitrile as well as in water leading to the almost complete conversion into lumiestrone.[8]Electron paramagnetic resonance spectroscopy using nitric oxide in the presence of estrone yielded a nitroxide radical signal very close to the one reported for cyclopentanone while nanosecond laser flash photolysis experiments showed that the conversion from estrone to lumiestrone was rapid. These results proved that 13α-epimerization of estrone was via the Norrish type I photocleavage of a cyclic ketone moiety.[8]

However, according to our knowledge, the direct irradiation (254 nm) of 3-acylestrones was not previously investigated making this one of our reason to develop the study. Therefore, based on the preliminary reports mentioned above and considering that the direct irradiation of estrone derivatives was not reported yet encouraged us to undertake more extensive work for which we chose 3-acetyl and 3-benzoylestrone as substrates (see Chart I).

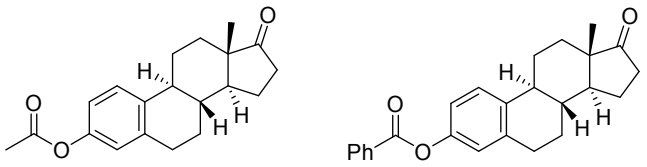
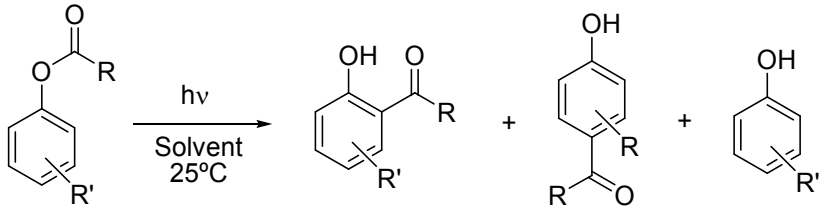


Chart I. Structures of the 3-acetylestrone (**1**) and 3-benzoylestrone (**2**).

Considering that estrone derivatives **1** and **2** bear an ester group on the phenyl ring, we were interested in studying the possible photo-Fries rearrangement induced by the direct irradiation (λ_{exc} = 254 nm) of these compounds. The photo-Fries rearrangement reaction was discovered by Anderson and Reese[9] and involves the homolytic cleavage of a carbon–heteroatom bond, *i.e.*, C-O,

C-S and C-N, of esters, thioesters and amides, respectively.[10] The product distribution of the photo-Fries rearrangement reaction is depicted in Scheme 2 for the case of aryl esters showing the *ortho*- and *para*-regioisomers as well as the corresponding phenols.[11] The radical mechanism of the photo-Fries rearrangement is well established and it is known that this rearrangement occurs mainly through the excited singlet state and the migration of the radical species takes place in the solvent cage.[12] However, most of the studies have been devoted to elucidating the mechanism of the reaction rather than its use in synthesis. Some examples regarding the application of the photo-Fries rearrangement in synthesis have been successfully employed in the preparation of griseofulvin, daunomycinone and flavonoids.[13] In addition, we have also contributed to the application of the photo-Fries reaction in the preparation of 2,2-dimethyl-4-chromanone derivatives and carbazole derivatives and recently, we have studied the effect of surfactant micelles on the photo-Fries reaction of a variety of substituted acetamides.[14]



R = alkyl or aryl
R' = electron donor and electron acceptor substituents

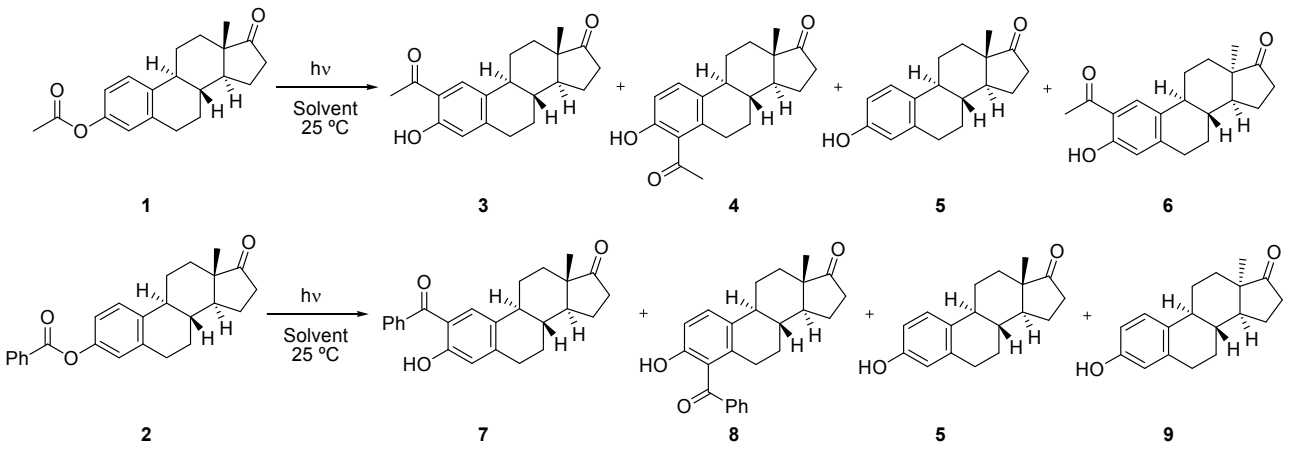
Scheme 2. The photo-Fries rearrangement of aryl esters.

Because direct irradiation of steroids was not been widely studied and taking into account that the photo-Fries rearrangement is an easy photochemical reaction to be performed, in the present work we examined the product distribution, triplet photosensitization and chemical quenching of the photochemical reactions of compounds **1** and **2** (see Chart I)**.**

Results.

Irradiation of 3-acetyl and 3-benzoylestrone in homogeneous media. Irradiation of 3-acetylestrone (**1**) in non-polar and polar solvents such as cyclohexane, MeOH and MeCN with λ_{exc}

= 254 nm under N_2 atmosphere provided the photoproducts expected from the photo-Fries rearrangement, viz. formation of the *ortho* regioisomers (**1a** and **1b** from 3-acetylestrone and **2a** and **2b** from 3-benzoylestrone), and estrone (**3**).We could also detect compound **4** in the reaction mixture from 3-acetylestrone and lumiestrone (**5**) was found in the reaction mixture after irradiation of 3-benzoylestrone. The photochemical reactions are depicted in Scheme 3.



Scheme 3.The photo-Fries rearrangement of 3-acetylestrone and 3-benzoylestrone (**1** – **2**).

The chemical yields of the photoproducts are collected in Table 1 and is apparent from the data that the [1;3]-migrated photoproducts, viz. compounds **3, 4** and **6** from ester **1** and **7** and **8** from ester **2,** are the main photoproducts when esters **1** and **2** are consumed in up to 98% yield. The migration of the acyl group occurred with a poor selectivity. However, the shift of the acyl group to position 2 of the aryl moiety is preferred over the migration of the same group to position 4 but depends on the reaction solvent. Indeed, in cyclohexane and MeCN the (**3**+**6**)/**4** and **7**/**8** ratios change from 3.1 to 4.9 while the ratios varied from 1 to 2 in MeOH. Steric effect due to the ring B of the steroid close to position 4 accounts for the low selectivity of the migration of the acyl group to position 4.

Table 1. Irradiation of 3-acyl estrones in different solvents under N_2 atmosphere. Yield of photoproducts[a] and reaction quantum yield (ϕ_R).[b]

3-Acyl estrones	Solvent	Yields (%)				ϕ_R
		3	**4**	**5**	**6**	
1	MeOH	27	23	9	20	0.01

	Cyclohexane	17	25	4	17	0.05
	MeCN	36	14	11	32	0.05
		7	**8**	**5**	**9**	ϕ_R
	MeOH	34	36	15	11	0.01
2	Cyclohexane	62	19	<1	ND[c]	0.01
	MeCN	47	15	<1	12	0.01

[a]Yield of photoproducts determined by ^{1}H-NMR spectroscopy in the reaction mixture. Concentration of 3-acyl estrone: 5.0×10^{-3} M. [b]Actinometer: KI (0.6 M), KIO_3 (0.1 M) and $Na_2B_2O_7.10H_2O$ (0.01 M) in water; $\phi(I_3^-) = 0.74$; $\lambda_{exc} = 254$ nm.;[15] Error: ± 0.01. [c]Not Detected.

The quantum yields of consumption (ϕ_R) of estrone derivatives (**1** and **2**) in non-polar and polar solvents were also measured (see Table 1). The ϕ_R values of esters **1** and **2** are 0.01 except for the irradiations ester **1** carried out in MeCN and cyclohexane, respectively, where the ϕ_R values are 0.05. However, these ϕ_R values imply that the photoreaction occurred smoothly and could compete with radiative and non-radiative pathways.

We employed UV-visible and NMR spectroscopies to follow the photochemical reaction. Figure 1(a) and (b) depict the time-resolved UV-visible absorption spectra of the photoreaction of 3-acetyl estrone (**5**) in cyclohexane and MeOH. A new absorption band located at 330 nm rises with irradiation time in both solvents. These bands were assigned to the *n*,π* transition of the carbonyl group of the *ortho*-rearranged photoproducts[16] and similar spectral behavior was also observed in MeCN. The *n*,π* transition band was not affected by a significant shift upon solvent polarity change.

Figure 1(c) represents the course of the photoreaction of ester **1** in MeOH measured by NMR spectroscopy where it is apparent that the acetyl [1;3]-migration to form the photoproducts **3, 4** and **6** is the main process. The relative yield profile was constructed recording the ^{1}H-NMR spectra of the reaction mixture at different irradiation times after evaporation of the reaction solvent and then dissolving the solid residue in deuterated chloroform. The aromatic protons of the steroid derivatives (**1**, **3**, **4**, **5** and **6**) were chosen as the diagnostic signals and after integration of these signals the yields were calculated. Similar results were obtained in cyclohexane and MeCN. Notably, the yield of estrone (**5**) was lower than 10% in all the solvents used. Figure 1(d) shows the

relative formation of the *ortho* regioisomers (**3, 4** and **6**) in polar and non-polar solvents. The relative rates of these photoproducts were similar in MeCN and cyclohexane while in MeOH was somewhat lower. The finding leads to the conclusion that in protic polar solvent radiative and non-radiative decay rates compete in a similar extent with the photoreaction pathway.

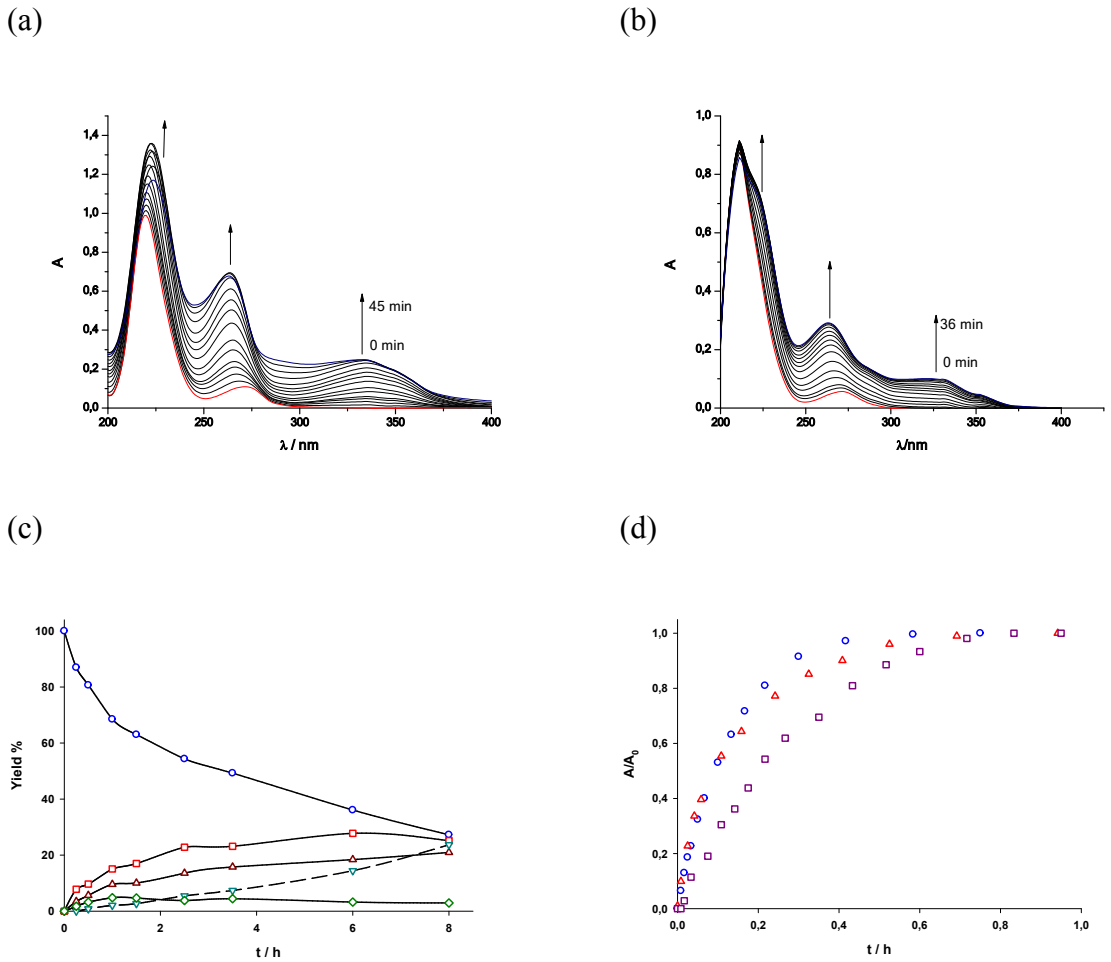


Figure 1. (a) UV-visible spectral change vs time of **1** in cyclohexane. Blue line: initial time; red line: 45min. (b) UV-visible spectral change vs time of **1** in MeOH. Blue line: initial time; red line: 36 min. (c) Relative yield profile vs time of **1** in MeOH: ester **1** (○); **3** (Δ);**4** (□ **); 5** (◊); **6** (▼). (d) Relative absorbance at 330 nm (A/A_∞) of formation of *ortho*-rearranged photoproducts (**3**, **4** and **6**) in: cyclohexane (○); MeCN (Δ); MeOH (□).

3-Benzoyl estrone (**2**) is characterized by a similar behavior compared to 3-acetyl estrone. Figure 2 resumes some representative spectroscopic results of its reactivity upon irradiation. The spectral change of the UV-visible absorption upon irradiation time (see Figure 2a) demonstrates that the photoreaction occurred efficiently. A new band located at 350 nm accounts for the formation of the photoproducts **7** and **8** and was assigned accordingly to the n,π^* electronic transition of the new

carbonyl groups formed during the irradiation. Likewise, ^{1}H-NMR spectroscopy of the reaction mixture at different irradiation times confirmed the main pathway of the reaction is the benzoyl [1;3]-migration that affords **7** and **8**. In addition, estrone (**5**) and lumiestrone (**9**) were also detected in the reaction mixture, and lumiestroneis formed with yields up to 12%.

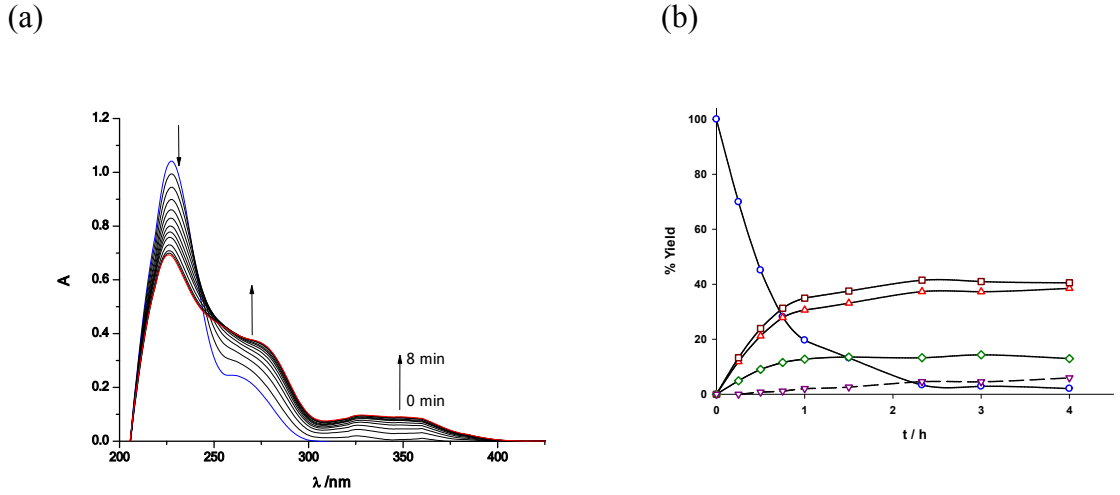
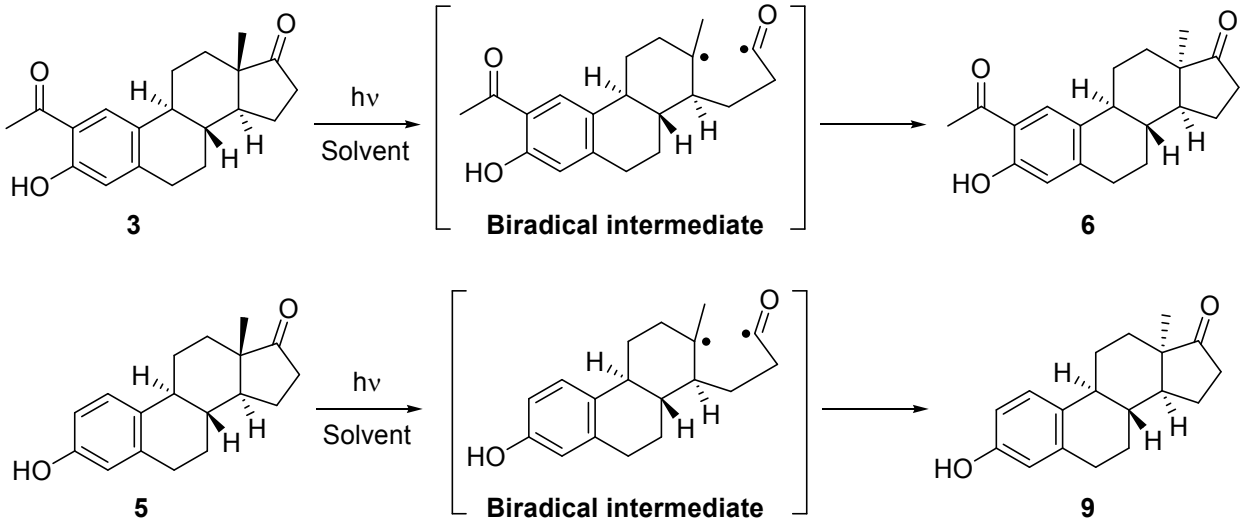


Figure 2. (a) UV-visible spectral change vs time of **2** in cyclohexane. Blue line: initial time; red line: 45 min. (b) Relative yield profile vs time of **2** in Cyclohexane: ester **2** (○); **7** (Δ); **8** (□); **5** (◊); **9** (▼).

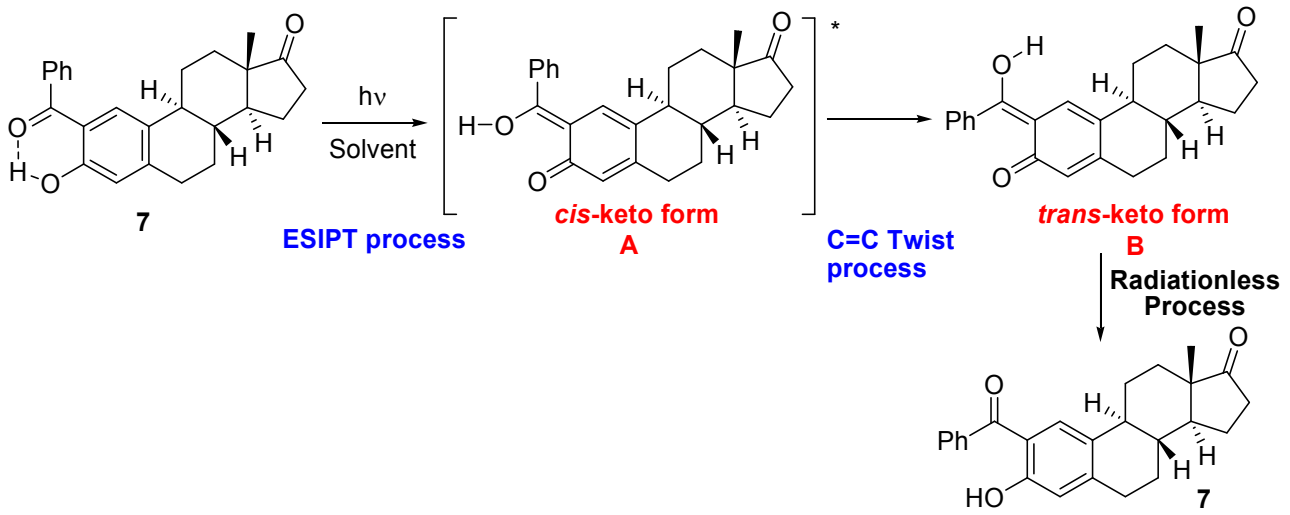
It is worth to mention that during the irradiation of 3-acetylestrone (**1**) the Norrish Type I photoreaction competes with the photo-Fries rearrangement. Epimerization of the methyl group at C-13 of photoproduct **3** was observed in polar and non-polar solvents (for example, see Figure 1c for the case of cyclohexane). Because photoproduct **3** is a chromophore and can absorb at 254 nm epimerization of methyl group occurred efficiently providing compound **6** which was formed with yields up to 32% (see Scheme 4).No epimerization of estrone and compound **4** was observed during irradiation of ester **1**. Likewise, we observed the Norrish Type I photoreaction also during the irradiation of 3-benzoyl estrone. On the other hand, estrone (**5**) is a chromophore able to absorb light, allowing it to epimerize to the corresponding lumiestrone (**9**) (see Scheme 4).[7,8]



Scheme 4. The Norrish Type I photoreaction of 2-acetylestrone (**3**) and estrone (**5**) in organic solvents.

The strong photostability observed for compounds **7** and **8** during irradiation of ester **2** can be ascribed to the formation of *trans*-keto tautomer in the ground state as it is depicted in Scheme 5 for the case of **7**. This tautomer is formed by the excited state intramolecular proton transfer (ESIPT)[17] of the *ortho*-regioisomer to produce the *cis*-keto tautomer in the excited state. The process is followed by deactivation with twisting of the newly produced C=C bond of the tautomer before intersystem crossing to the triplet excited state occurs. This radiationless process of the *cis*-keto tautomer gives the *trans*-keto tautomer in its ground state. This behavior is usually observed with β-hydroxy carbonyl compounds such as 2'-hydroxychalcones in π,π* excited states, where the phenolic group usually becomes more acidic and the carbonyl more basic. The ensuing enhancement of the proton transfer favors the one-way *cis-trans* isomerization of 2'-hydroxychalcones.[18] Compounds **7** and **8** have a β-hydroxy carbonyl and can absorb light of 254 nm, the ESIPT process causes the deactivation through radiative and non-radiative pathways. Consequently, no Norrish Type I photoreaction does compete with these pathways. Therefore, epimerization of these photoproducts was not observed upon irradiation of ester **2**. In the case of 3-acetyl estrone (**1**), photoproduct **4** showed similar behavior as it was described for photoproducts **7** and **8** while compound **3** epimerized efficiently providing **6** with yields up to 32%. This distinct

behavior showed by compound **3** can be attributed to the non-planarity of the acetyl group with the benzene moiety partially preventing the intramolecular hydrogen bonding between the carbonyl group and the hydroxyl group. Therefore, the ESIPT process is not a competitive pathway, and epimerization reaction of the carbonyl group at C-17 occur smoothly providing compound **6**. Furthermore, intramolecular triplet photosensitization from the aryl moiety to the carbonyl group at C-17 of compound **6** is the source of the observed epimerization, in accordance with was reported in the literature for the case of 3α-dimethylphenylsilyloxyandrostanone derivatives.[6g,19]



Scheme 5. *Cis-trans* keto tautomerism of compound **7**.

Photosensitization and chemical quenching of the photo-Fries rearrangement of estrone derivatives. In order to determine the multiplicity of the excited state involved in the photo-Fries rearrangement, 3-benzoyl estrone (**2**) was chosen as the triplet energy acceptor probeand acetone was chosen as the triplet energy donor. This selection lies on the known triplet energies (E_T) values. The E_T of acetone[20] is 74 kcal.mol^{-1} while 3-benzoyl estrone's one was assumed to be similar to that of estrone (69.4 kcal.mol^{-1})[21], considering the benzoyl group does not influence substantially the value. Therefore, the triplet energy transfer pathway was a thermodynamically feasible process because the energy gap between the triplet energy values was *ca.*5 kcal.mol^{-1}. Then, photosensitization of 3-benzoyl estrone was carried out in acetone with λ_{exc} = 310 nm and the

results are shown in Table 2. It is apparent from the data collected in the table that photosensitization of estrone **2** with acetone occurs smoothly providing the *ortho*-regioisomers **7** and **8** in yields lower compared to the same experiment carried out in MeOH while the yield of estrone **5** was doubled. Noteworthy, the formation of lumiestrone **9** was not enhanced under acetone photosensitization.

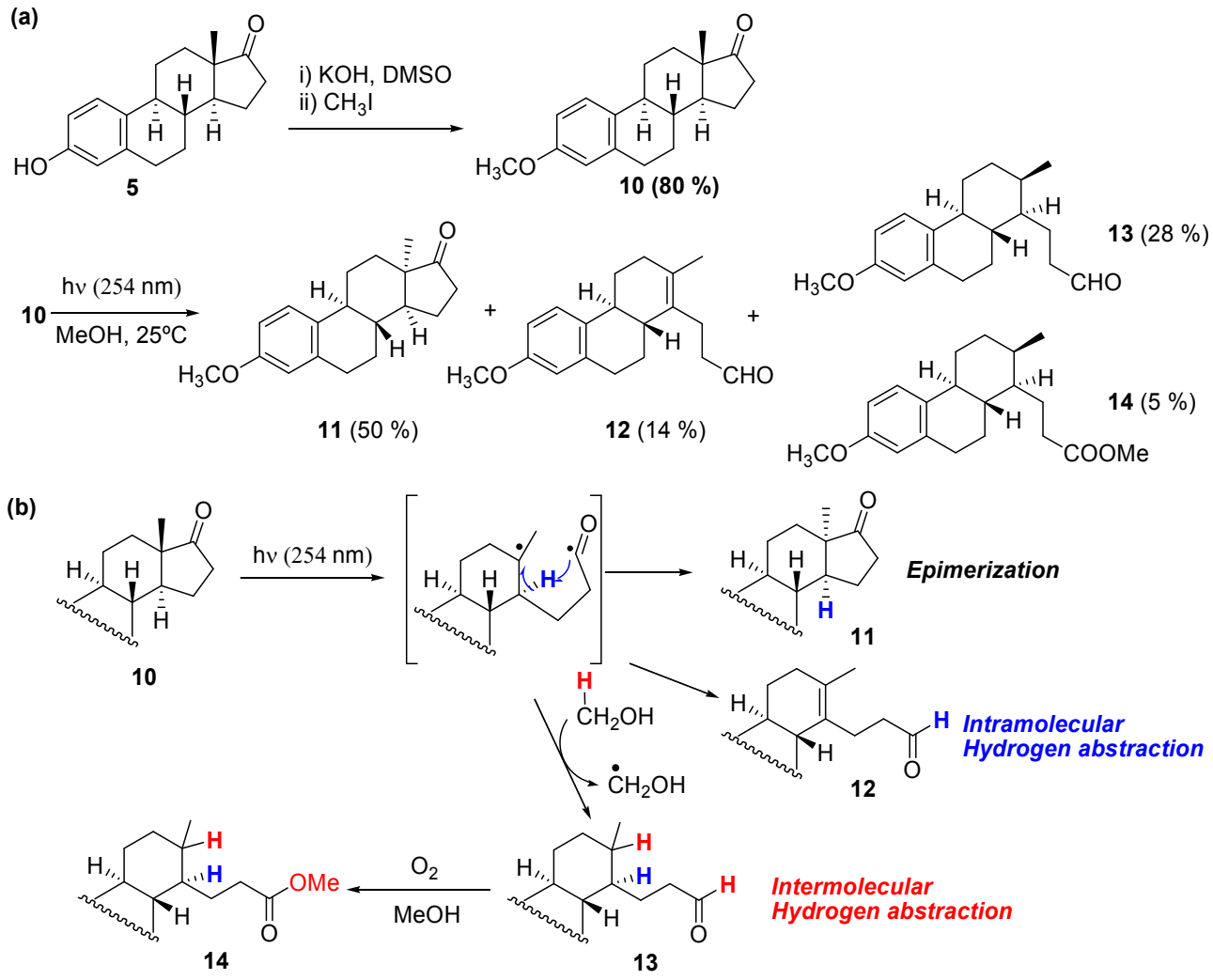
Tetramethyl-1,2-diazetine dioxide (TMDO) was chosen as the triplet energy quencher (E_T = 54.0 kcal.mol^{-1})[14e]owing to the energy gap between its triplet state and the one estrone **2** (*ca.* 15 kcal.mol^{-1} lower than **2**).A thermodynamically feasible triplet energy transfer pathway between these species is hence possible. Consequently, the irradiation of 3-benzoyl estrone **2** in MeOH in the presence of increasing amounts of TMDO, the triplet energy quencher, the photo-Fries rearrangement took place efficiently while the formation of lumiestrone **9** diminished significantly (see Table 2). These results suggest that in the photo-Fries reaction the excited triplet state is not the photoreactive state while the epimerization reaction of estrone **5** to lumiestrone **9** involves the triplet excited state because TMDO quenches the reaction efficiently. These results match with the ones present in the literature, demonstrating the involvement of a triplet excited state in the photo epimerization reaction of cyclic ketones.[6g,19,22]

Table 2. Irradiation of 3-benzoyl estrone in methanol, acetone and the presence of TMDO under N_2atmosphere.[a]

Estrone	Solvent	Additive	Yields (%)			
		TMDO[b] (mol.dm^{-3})	**7**	**8**	**5**	**9**
2	MeOH	----	34	36	15	11
	Acetone[c]	----	22	14	29	13
	MeOH	5.0x10^{-4}	27	31	18	2
		1.0x10^{-3}	23	23	10	1
		1.5x10^{-3}	23	16	3	---

[a]Yield of photoproducts determined by ^{1}H-NMR spectroscopy in the reaction mixture. Concentration of 3-benzoyl estrone: 1.0x10^{-3} M. Irradiation with λ_{exc} = 254 nm. [b]Tetramethyl-1,2-diazetina dioxide. [c]Irradiation with λ_{exc} = 310 nm.

We decided to synthesize estrone methyl ether (**10**) as a way to assess whether the photo epimerization of estrone **5** takes place from the triplet excited state through a Norrish type I mechanism. Methylation of estrone (**5**) with KOH / DMSO / MeI (see Scheme 6)[23] afforded compound **10** that was fully characterized using physical and spectroscopic methods. Irradiation of estrone**6** in methanol with λ_{exc} = 254 nm under N_2 atmosphere gave the lumiestrone methyl ether (**11**) as the main photoproduct in 50 % yield along with compounds **12**, **13** and **14** (see Scheme 6).



Scheme 6.(a) Preparation and irradiation of estrone methyl ether **10**. (b) Plausible reaction mechanism.

Direct irradiation of estrone methyl ether (**10**) demonstrates that photo epimerization of methyl group at C-13 occurs efficiently through a Norrish type I mechanism involving a biradical intermediate (see Scheme 6(b)). Additionally, the formation of compounds **12** and **13** accounts for inter- and intramolecular hydrogen abstraction from the same intermediate (Scheme 6(b)).

Oxidation of compound **13** by residual molecular oxygen present in the reaction mixture afforded the corresponding carboxylic acid that, in turn, reacted with MeOH to give compound **14**.

Triplet quenching of the photoreaction of estrone methyl ether (**10**) with TMDO in methanol under N_2 atmosphere was also carried out, assuming that the triplet energy of estrone methyl ether is *ca.* 70 kcal mol^{-1}, which is similar to that of estrone[21] or 17β-estradiol[24]. The results are summarized in Table 3.

Table 3. Irradiation of estrone methyl ether (**10**) in methanol in the presence of TMDO under N_2atmosphere.[a]

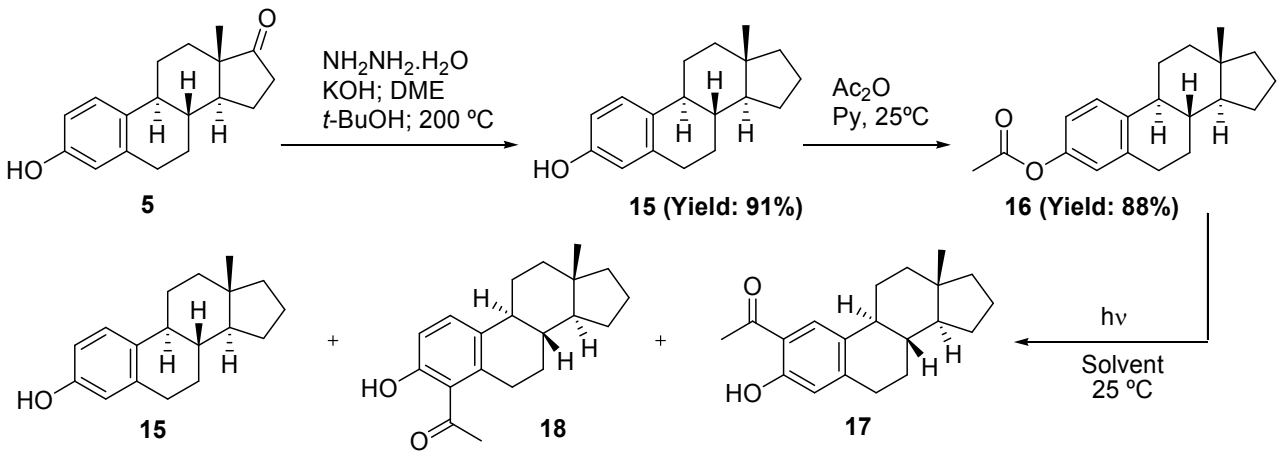
TMDO[b] (mol dm^{-3})	Yield of 11 (%)	Conversion (%)
0	55	91
$5.0x10^{-4}$	52	69
$1.0x10^{-3}$	31	38
$1.5x10^{-3}$	24	29

[a]Yield of photoproducts determined by ^{1}H-NMR spectroscopy in the reaction mixture. Concentration of 3-methoxy estrone: $1.0x10^{-3}$ M. Irradiation with λ_{exc} = 254 nm. [b]Tetramethyl-1,2-diazetina dioxide.

As can be seen in Table 3 it is apparent that TMDO quenches efficiently the photo epimerization reaction of estrone methyl ether **10** confirming that the photo reaction takes place from the triplet excited state. Photosensitization of estrone methyl ether **10** in acetone (λ_{exc} = 310 nm) provided compound **11** as the sole product demonstrating again that the triplet excited state is involved in the epimerization reaction. In this experiment, acetone is both the solvent and the photosensitizer.

Irradiation of 3-acetyl 17-norestrone (16) in homogeneous media. In order to demonstrate that the carbonyl group (C-17) is responsible of the competitive Norrish type I reaction during the irradiation of estrones **1** and **2**, we decided to prepare 3-acetyl 17-norestrone **16** as a probe compound. The preparation of compound **16** starts with the reaction of estrone **5** under Wolf-Kischner conditions in dimethoxy ethane at 200 °C providing17-norestrone **15** in good yield. After purification by column chromatography, compound **15** was acetylated with acetyl anhydride in

pyridine at room temperature giving compound **16** in 88% yield (see Scheme 7). Both compounds **15** and **16** were fully characterized by means of physical and spectroscopic methods.



		Yield (%)			
Solvent	**Conv. (%)**	**17**	**18**	**15**	**ϕ_R**
MeOH	87	60	23	4	0.16
Cyclohexane	81	46	35	1	0.15

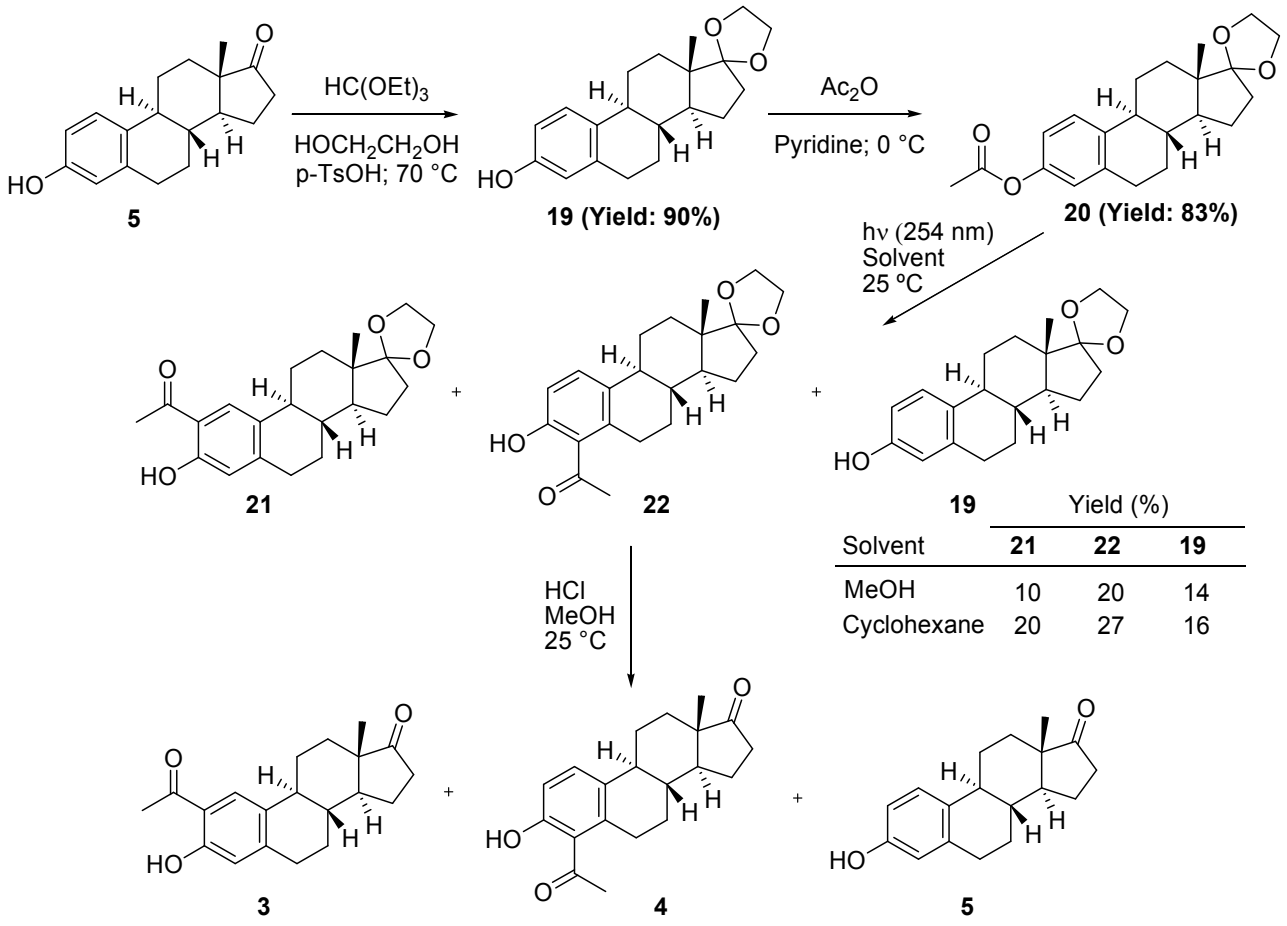
Scheme 7. Preparation and irradiation of 3-acetyl 17-norestrone **16**.

Irradiation of 3-acetyl-17-norestrone (**16**) in MeOH and cyclohexane (λ_{exc} = 254 nm) under N_2 atmosphere provided the expected photoproducts from the photo-Fries rearrangement, viz. formation of the *ortho*-regioisomers (**17** and **18**) and 17-norestrone (**15**) (see Scheme 7). No epimerization of the photoproducts was observed because compound **16** does not bear a carbonyl group at C-17. We determined the chemical yields using NMR spectroscopy and compounds **17** and **18** were the main photoproducts when the ester **16** was consumed in up to 87% yield (see Scheme 7). The selectivity of the acetyl migration depended on the reaction solvent used and the **17**/**18** ratio was found to be 2.6 in MeOH while in cyclohexane was found to be 1.4. The photoreaction was also followed by UV-visible spectroscopy and a new band located at 330 nm rises with irradiation time (see Figure S1 in Supporting Information) which was assigned to the n,π^* transition of the carbonyl group of the *ortho*-rearranged photoproducts.[16]

The quantum yields of consumption (ϕ_R) of **16** were measured in MeOH and cyclohexane (see Scheme 7) and were found to be similar in both solvents (*ca.* 0.16). Notably, ester **16** showed a ϕ_R

value16 times higher than ester **1** when the irradiation solvent was MeOH whereas in cyclohexane, the ϕ_R value was found to be 3 times higher than ester **1**. This photochemical behavior can be attributed to the absence of the carbonyl group at C-17 in ester **16** and, therefore, no competition between the photo-Fries rearrangement and the antenna sensitization of the aryl moiety takes place during the irradiation.

Preparation of 2-acetyl estrone (3) and 4-acetyl estrone (4) applying the photo-Fries rearrangement. Having understood the mechanistic facets involving the irradiation of **1**, we aimed to prepare estrone derivative **3** without epimerization of ring D (see Scheme 8).[25]Estrone **5** was reacted with triethylorthoformate and ethylene glycol in the presence of *p*-toluenesulfonic acid at 70 °C providing estrone derivative **19** in 90% yield. Then, acetylation of compound **19** with acetic anhydride in pyridine gave compound **16** in 83%yield. Both intermediates, viz. **19** and **20**, were fully characterized by means of NMR spectroscopy.



	Yield (%)		
Solvent	**21**	**22**	**19**
MeOH	10	20	14
Cyclohexane	20	27	16

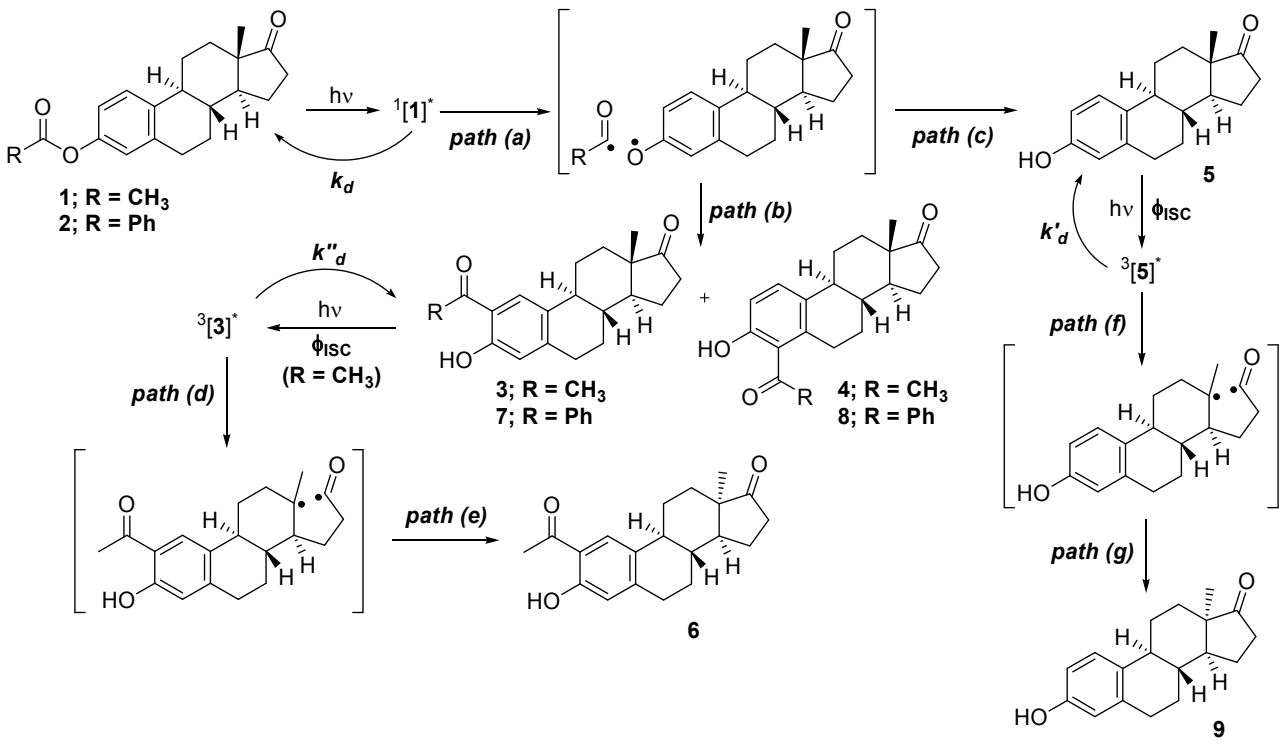
Scheme 8. Preparation and irradiation of compound **20**.

Irradiation of compound **20** in polar and non-polar solvents such as MeOH and cyclohexane with λ_{exc} = 254 nm under N_2 atmosphere provided the expected photoproducts from the photo-Fries rearrangement, viz. formation of the *ortho* rearranged protected photoproducts (**21** and **22**), and protected estrone (**19**) (see Scheme 8). No epimerization of the photoproducts was observed and the chemical yields in both solvents were determined by NMR spectroscopy (see Scheme 8). No significant selectivity was observed for the migration of the acetyl group in both reaction solvents used to perform the photoreaction. Indeed, the **22:21** ratio was found to be 2:1 when the solvent was methanol while in cyclohexane the **22**:**21** ratio was found to be ca. 1.4:1. On the other hand, the quantum yield of consumption (ϕ_R) of ester **20** was also measured and the values depended on the nature of the solvent, *i.e.* in cyclohexane the ϕ_R values was found to be 0.02 while in methanol was doubled (ϕ_R = 0.04). These values are in the same order of magnitude of those obtained for the irradiations of ester **1** and **2** (see Table 1). The last step involved in the synthetic approach was the deprotection reaction of photoproducts **21** and **22** under acid catalysis in methanol at room temperature. This reaction was found to be quantitative providing products **3** and **4** in a clean process. Also, deprotection of compound **19** under the abovementioned acidic conditions provided estrone **5** in quantitative yield.

Discussion.

As hinted above, 3-acetyl- and 3-benzoyl estrone, **1** and **2**, respectively, reacted efficiently upon direct irradiation (254 nm) in homogeneous media (cyclohexane, MeCN and MeOH) under N_2 atmosphere (see Scheme 1 and Figures 1 and 2) providing the [1;3]-migrated photoproducts along with estrone (see Table 1). However, epimerization reaction of **3** to give compound **6** occurred during the irradiation of 3-acetyl estrone (**1**) while lumiestrone (**9**) was formed upon irradiation of 3-benzoyl estrone (**2**). This behaviour shows that two reaction pathways operate during the irradiation of 3-acyl estrone: i) the photo-Fries rearrangement reaction and, ii) the Norrish type I

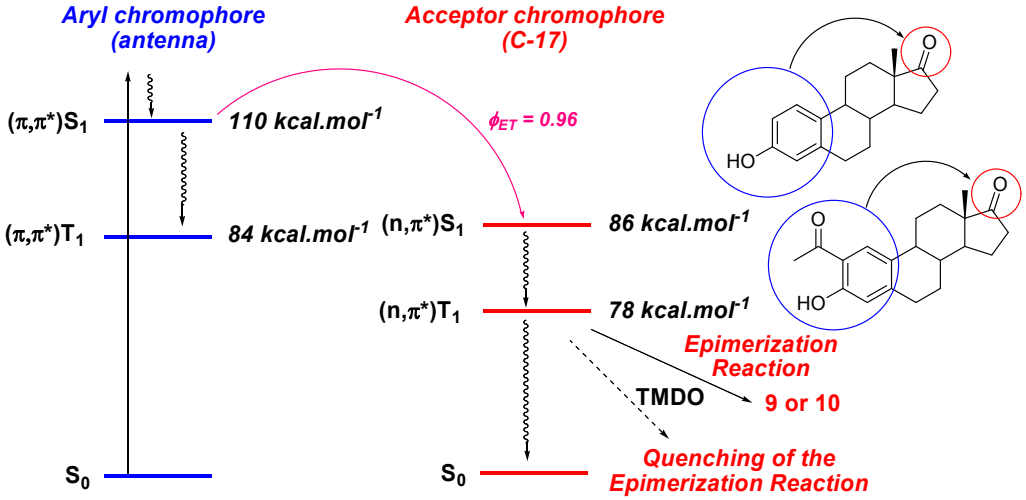
reaction. On the basis of our results, a reaction mechanism for the irradiation of 3-acyl estrone is proposed in Scheme 9.



Scheme 9. The reaction mechanism of compounds **1** and **2**.

Irradiation of 3-acyl estrone (**1** and **2**) with 254 nm light-source populates the singlet excited state which is the photo reactive excited state. The triplet excited state is not involved in the photo-Fries rearrangement of 3-acyl estrones as it was evidenced by the triplet quenching experiments with **2** in the presence of TMDO (see Table 2). Then, homolytic fragmentation of the ester group (***path (a)***) occurs efficiently from the singlet excited state and competes with radiative and radiationless processes from the same excited state (k_d). After C(O)-O bond cleavage, the acyl and phenoxy radicals are formed in the solvent cage and these species evolve to photoproducts through two competitive pathways (***paths (b)*** and ***(c)*** in Scheme 9). Thus, in-cage [1;3]-migration of the acyl radicals to positions 2 and 4 affords the expected *ortho*-regioisomers **3** and **4** from ester **1** and **7** and **8** from ester **2** (***path (b)***). On the other hand, diffusion of the radical species from the solvent cage was another viable pathway. Indeed, estrone (**5**) is formed after hydrogen atom abstraction of the phenoxy radical from the solvent (***path (c)***). Noteworthy, the *ortho*-regioisomers **4**, **7** and **8** were

photo stable compounds upon irradiation with λ = 254 nm. This strong photo stability is attributed to the excited state intramolecular proton transfer (ESIPT)[17] process between the proton of the hydroxyl group and the carbonyl group attached to the aromatic ring (see Scheme 5) and a *cis-trans* keto tautomerism accounts for this behavior where radiation and radiationless processes are the sole deactivation pathways of the *ortho*-regioisomers. However, compound **3** undergoes photo-epimerization reaction resulting in compound **6**. This photochemical reactivity is ascribed to the out-of-plane deviation of the acetyl group from the planarity of the aromatic ring disfavoring the intramolecular proton transfer process and the *cis-trans* keto tautomerism. Direct irradiation of compound **3** with 254 nm populated the triplet excited state of the carbonyl group (C-17) at the D ring of the steroid because a singlet-singlet energy transfer between the aryl moiety and the carbonyl group (C-17) occurred efficiently (see later in the text).[21] Deactivation of the triplet state through radiationless process (k''_d in Scheme 9) restores **3** in the ground state. Competitively, a Norrish Type I photoreaction is a competitive deactivation process for triplet excited state of **3**. Thus, fragmentation of the C_α-C=O bond at the ring D of compound **3** (***path (d)***) provides the biradical intermediate that, epimerizes the methyl group at C-13 giving compound **6** (***path (e)***). Similar conclusions can be drawn for estrone**3** that is converted to lumiestrone **9** (***paths (f)*** and ***(g)*** in Scheme 9) through a Norrish Type I reaction.[6g,19,22] The results obtained in the presence of increasing amounts of TMDO confirm that the Norrish Type I photoreaction of **10** to give lumiestrone methyl ether **11** is inhibited. The finding supports the involvment of a triplet excited state located on the carbonyl group (C-17) of the D ring of the steroid as the photo reactive state (see Scheme 6 and Table 3) for this process to occur. The same conclusions can be drawn analyzing the results of the photosensitization (λ = 310 nm) of compound **10** with acetone. The reaction demonstrates that the triplet excited state is involved in the epimerization reaction and product **11** was the sole photoproduct formed. The photochemical behavior described for compounds **3**, **5** and **10** regarding the Norrish Type I reaction and consequently, the epimerization of the C-13 methyl group are depicted in Scheme 10.



Scheme 10. Plausible mechanism for intramolecular energy transfer for aryl antenna to the C17-keto group of estrone (**5**).

Some time ago, Weinreb and Werner[21] have intensely studied the photophysics of a series of estrogen derivatives and, mainly, they found that estrone was able to give fluorescence emission from both the phenolic moiety (λ_{em} = 284 nm) and the carbonyl group (C-17) (λ_{em} = 412 nm). The only way to explain this photo physical behavior was attributed to the singlet-singlet energy transfer from the singlet state of the phenolic moiety to the carbonyl group. Indeed, this energy transfer process was found to proceed with a quantum yield of 0.96 and a rate constant of 2.4×10^9 s^{-1}, a value higher than the intersystem crossing process of the phenolic moiety. Therefore, excitation to the singlet excited state of the phenolic moiety (the *antenna* chromophore in Scheme 10) populates efficiently the singlet excited state of the carbonyl group (C-17; the *acceptor* chromophore in Scheme 10) because it is a feasible thermodynamic process. Once this latter excited state is reached, fluorescence emission competes with the intersystem crossing process and the triplet excited state (n,π^*) of the carbonyl group is formed. Finally, C(O)-C_α bond cleavage occurs, and epimerization reaction of the methyl group took place smoothly through a Norrish Type I fragmentation reaction. Alternatively, energy transfer from the $T_1(\pi,\pi^*)$ of the phenolic moiety to the $T_1(n,\pi^*)$ of the carbonyl group cannot be ruled out. However, Weinreb and co-workers have stated that this process does not proceed efficiently.[21] A similar Jablonski diagram can be proposed and, we are also

convinced that operates satisfactorily, for estrone methyl ether (**6**) and *ortho*-regioisomer **3**. Therefore, the epimerization reaction of these compounds occurs from the triplet excited state ($T_1(n,\pi^*)$) of the carbonyl group and it was demonstrated that physical quenching of the epimerization reaction with TMDO, a triplet quencher, proceeds efficiently.

Direct irradiation of 3-acetyl-17-norestrone (**16**) with light of 254 nm in MeOH and cyclohexane gave the *ortho*-regioisomers **17** and **18** in good yield but with a noticeable regioselectivity in favor of compound **17** (see Scheme 7). However, no epimerization reaction of *ortho*-regioisomer **17** as well as 17-norestrone (**15**) was observed because both compounds do not bear a carbonyl group at C-17 and, as a consequence, the Norrish Type I reaction has no chance to compete with the photo-Fries rearrangement. Indeed, the photo-Fries reaction of compound **16** occurred with quantum yields (ϕ_R) higher than those observed for esters **1** and **2** in the same solvent (compare the data shown in Scheme 7 and Table 1). Taking into account this photochemical behavior we reasoned that if the carbonyl group at C-17 of compound **1** would be protected as a 1,3-dioxolane derivative and then acetylated (compounds **19** and **20** in Scheme 8, respectively) no competition of the Norrish Type I would occur during the photo-Fries rearrangement of compound **20**. Indeed, irradiation of **20** provided efficiently the *ortho*-regioisomers **21** and **22** in good yield without epimerization of methyl group at C-13 (see Scheme 8). In a second step, deprotection of the *ortho*-regioisomers **21** and **22** under acid catalysis gave the desired 2-acetyl- (**3**) and 4-acetyl estrone (**4**) derivatives in quantitative yield. This synthetic approach showed that in only four steps the *ortho*-regiosiomers **3** and **4** were prepared in good yields from estrone as the starting material, with no side epimerization. In this synthetic scheme, the application of the photo-Fries reaction onto compound **20** represents the crucial step. We suggest that this methodology would be useful in the preparation of other kinds of steroid derivatives belonging to the family of estrone.

Conclusions.

The photochemical reaction of 3-acyl estrone examined in this paper takes place efficiently providing the expected *ortho*-regioisomers and estrone through the photo-Fries rearrangement. Photosensitization and chemical quenching demonstrate that the photoreaction occurs from the singlet excited state. The formation of the *ortho*-regioisomers depends on the solvent reaction and a noticeable regioselectivity is observed in favor of 2-acetyl estrone derivatives. The C-O homolytic cleavage that gives in-cage acyl and phenoxyl radicals competes with radiative and radiationless excited state deactivation pathways. These radicals can couple in the solvent cage to give the desired *ortho*-regioisomers (**3**, **4**, **7** and **8** in Scheme 9) through a [1;3]-acyl migration process or can diffuse to the bulk and give estrone. Compounds **4**, **7** and **8** were found to be photo stable photoproducts due to the efficient ESIPT processes under UV irradiation (see Scheme 5). On the other hand, estrone, the *ortho*-regioisomer (**3**) and estrone methyl ether (**10**) are found to epimerize upon irradiation with UV light (254 nm) through a Norrish Type I mechanism (see Schemes 4 and 9). This photoreaction involves the triplet excited state of the carbonyl group (C-17) at the D ring of the steroids that is populated from the singlet excited state of the phenolic moiety through an intramolecular energy transfer process (see Scheme 10). Finally, a four step reaction sequence was applied to prepare the *ortho*-regiosiomers **3** and **4** in good yields, starting from estrone and avoiding the epimerization of methyl group (C-13) of the D ring of the estrone moiety (see Scheme 8). This synthetic approach shows that application of the photo-Fries reaction of compound **20** is an alternative step to avoid the photo epimerization reaction of compound **3** to compound **6** (see Scheme 3), suggesting its utility in organic synthesis. Further studies on the photo-Fries reaction of 3-alkyl and 3-aryl sulfonyloxyestrone derivatives are currently in progress in our laboratory and will be reported in due course.

Experimental.

Materials and equipment. Estrone, acetyl chloride, acetic anhydride, benzoyl chloride, pyridine, tetramethyl-diazodiazetine dioxide and acetone were obtained from commercial sources.

Spectroscopic grade solvents were used as received. Pyridine was distilled and stored over KOH pellets. Melting Points were determined with a Fisher Jones apparatus and are not corrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$on a 500 MHz spectrometer; chemical shifts (δ) are reported in parts per million (ppm), relative to signal of tetramethylsilane, used as internal standard. 2D NMR spectra (HSQC and HMQC sequences) were recorded in $CDCl_3$ on a 500 MHz spectrometer. Coupling constant (*J*) values are given in Hz. The measurements were carried out using standard pulse sequences. The UV-visible spectra were measured with a Shimadzu UV-1203 spectrophotometer using two-faced stoppered quartz cuvettes (1 mm x 1 mm) at 298 K. HR-MS (ESI) analyses were performed on a Bruker micrOTOF-Q-11 instrument. Quadrupole – time of flight analyzer that provides exact masses with an error less than 3 ppm in EM and less than 5 ppm in EM/MS.

General procedure for the synthesis of esters 1 and 2. To a solution of estrone (1.85 mmol) in pyridine (10 mL) chilled in an ice-bath, acetic anhydride for **1** or benzoyl chloride for **2** (2.22 mmol) was added dropwise 10 min under stirring. After the addition of the acylating reagents, the solution was stirred at 25 ºC until TLC control showed total consumption of estrone. Then, the reaction mixture was extracted with dichloromethane (10 mL) and washed with a solution of diluted HCl (10 mL). The organic phase was then washed three times with water, dried over Na_2SO_4, filtrated and evaporated under vacuum. The solid residue was washed with 10 ml of cold methanol (0/5 °C) and dried in the air. The corresponding esters were obtained in excellent yields (>90%). Compounds **1** and **2** were characterized by comparison with the physical constant (m.p.) and spectroscopic data (^{1}H and ^{13}C NMR) reported in the literature.

17-Oxoestra-1,3,5(10)-trien-3-yl acetate (**1**). White solid (0.54 g, 93%). M.p.: 126 - 127ºC (lit. 125 - 126ºC[26]). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.5 Hz, 1H, H-1), 6.85 (dd, *J* = 8.5, 2.6 Hz, 1H, H-2), 6.81 (d, *J* = 2.6 Hz, 1H, H-4), 2.94 – 2.86 (m, 2H, H-6), 2.51 (dd, *J* = 19.0, 8.8 Hz, 1H, H-16), 2.43 – 2.38 (m, 1H, H-11), 2.32 – 2.25 (m, 1H, H-9), 2.28 (s, 3H, H-20), 2.14 (dt, *J* = 18.6,

8.9 Hz, 1H, H-16'), 2.09 – 1.94 (m, 3H, H-12, H-7 and H-15), 1.68 – 1.40 (m, 6H, H-7', H-14, H-8, H-12', H-11' and H-15'), 0.91 (s, 3H, H-18).$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$):δ 220.8 (C-17), 169.9 (C-19), 148.6 (C-3), 138.1 (C-5), 137.5 (C-10), 126.5 (C-1), 121.7 (C-4), 118.8 (C-2), 50.5 (C-14), 48.1 (C-13), 44.3 (C-9), 38.1 (C-8), 35.9 (C-16), 31.6 (C-12), 29.5 (C-6), 26.4 (C-11), 25.8 (C-7), 21.7 (C-15), 21.2 (C-20), 13.9 (C-18).

17-Oxoestra-1,3,5(10)-trien-3-yl benzoate (**2**). White solid (0.67 g, 95%). M. p.: 217-219ºC (lit. 217 - 220ºC[27]).^1H NMR (500 MHz, $CDCl_3$):δ 8.20 (d, *J*=7.53 Hz, 2H, H-22), 7.67 – 7.60 (t, 1H, *J* = 7.3 Hz, H-24), 7.51 (t, *J* = 7.7 Hz, 2H, H-23), 7.34 (d, *J* = 8.5 Hz, 1H, H-1), 6.99 (dd, *J* = 8.4, 2.6 Hz, 1H, H-2), 6.95 (d, *J* = 2.6 Hz, 1H, H-4), 2.98 – 2.92 (m, 2H, H-6), 2.52 (dd, *J* = 19.1, 8.7 Hz, 1H, H-16), 2.43 (dq, *J* = 11.5, 3.1, 2.1 Hz, 1H, H-11), 2.32 (td, *J* = 10.9, 3.8 Hz, 1H, H-9), 2.16 (dt, *J* = 18.6, 8.8 Hz, 1H, H-16), 2.10 – 1.96 (m, 3H, H-12, H-7 and H-15), 1.70 – 1.43 (m, 6H, H-7', H-14, H-8, H-12', H-11' and H-15'), 0.93 (s, 3H, H-18).$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$):δ 220.9 (C-17), 165.6 (C-20), 148.9 (C-3), 138.2 (C-5), 137.5 (C-10), 133.6 (C-24), 130.2 (C-22), 129.7 (C-21), 128.6 (C-23), 126.6 (C-1), 121.8 (C-4), 119.0 (C-2), 50.5 (C-14), 48.1 (C-13), 44.3 (C-9), 38.1 (C-8), 36.0 (C-16), 31.7 (C-12), 29.5 (C-6), 26.5 (C-11), 25.9 (C-7), 21.7 (C-15), 13.9 (C-18).

General procedure for the synthesis of estrone methyl ether (10). Powdered KOH (21.7 mmol) was added to DMSO (12 ml) and the solution was stirred for 5 min. Then, estrone (5.5 mmol) was added to the solution followed by the addition of MeI (11 mmol). The reaction mixture was stirred for *ca*. 1 hr until TLC control showed total consumption of estrone. The reaction mixture was poured into water (100 ml) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water, dried over Na_2SO_4, filtrated and evaporated under vacuum. The white solid residue was recrystallized from ethyl acetate to give the desired compound **10**.

3-Methoxyestra-1,3,5(10)-trien-17-one (**10**). White solid (4.94 g, 80 %). M.p.: 143-145ºC (lit. 142ºC[28]). ^1H NMR (500 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 8.6, 1.1 Hz, 1H, H-1), 6.72 (dd, *J* = 8.6, 2.8 Hz, 1H, H-2), 6.65 (d, *J* = 2.8 Hz, 1H, H-4), 3.78 (s, 3H, CH_3O), 2.96 – 2.85 (m, 2H, H-6), 2.50 (ddd, *J* = 19.0, 8.8, 0.9 Hz, 1H, H-16), 2.43 – 2.37 (m, 1H, H-11), 2.26 (td, *J* = 10.7, 4.4 Hz, 1H, H-

9), 2.14 (dt, *J* = 18.9, 8.9 Hz, 1H, H-16), 2.09 – 1.92 (m, 3H, H-12, H-7 and H-15), 1.68 – 1.37 (m, 6H, H-7', H-14, H-8, H-12', H-11' and H-15'), 0.91 (s, 3H, H-18). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 221.1 (C-17), 157.7 (C-3), 137.9 (C-5), 132.1 (C-10), 126.4 (C-1), 114.0 (C-4), 111.7 (C-2), 55.3 (C-19), 50.5 (C-14), 48.1 (C-13), 44.1 (C-9), 38.5 (C-8), 36.0 (C-16), 31.7 (C-12), 29.8 (C-6), 26.7 (C-7), 26.0 (C-11), 21.7 (C-15), 14.0 (C-18).

General procedure for the synthesis of estra-1,3,5(11)-trien-3-ol (14) and estra-1,3,5(10)-trien-3-yl acetate (16). To a solution of 0.51 g of KOH (9.25 mmol) in 3.5 ml of diethylene glycol was added a solution of 0.5 g of estrone (1.85 mmol) in butanol and 0.28 g of hydrazine hydrate (5.6 mmol). After refluxing the reaction mixture for about 0.5 h the mixture water-butanol was drained from the condenser and the temperature allowed rising to 200 °C while refluxing was continued for additional 2 hr. Then, the reaction mixture was cooled, diluted with water and poured slowly into 2 ml of 6 N HCl solution. An amorphous solid separated from the solution which was filtered, washed with cold water and finally, purified by flash chromatography on silica gel with hexane and ethyl acetate mixtures to give compound **15**. Acetylation of compound **15** with acetic anhydride in pyridine was performed by the procedure previously described giving compound **16** as a white solid after purification by flash chromatography on silica gel with hexane and ethyl acetate mixtures.

Estra-1,3,5(10)-trien-3-ol (**15**). White solid (0.45 g, 91%). M.p.: 134 - 135ºC (lit. 134 - 134.5ºC[25a]).^{1}H NMR (500 MHz, $CDCl_3$):δ 7.17 (d, *J*=8.38 Hz, 1H, H-1), 6.63 (dd, *J*= 2.79 and 8.42 Hz, 1H, H-2), 5.57 (d, *J*=2.61 Hz, 1H, H-4), 2.77-2.89 (m, 2H, H-6), 2.16-2.30 (m, 2H), 1.05-1.94 (m, 13H), 0.75 (s, 3H, H-18). $^{13}C\{^{1}H\}$NMR (126 MHz, $CDCl_3$):δ 153.2 (C-3), 138.5 (C-5), 133.4 (C-10), 126.7 (C-1), 115.4 (C-4), 112.7 (C-2), 53.7 (C-14), 44.2 (C-9), 41.2 (C-13), 40.6 (C-17), 39.3 (C-8), 38.9 (C-12) , 29.9 (C-6), 28.2 (C-7), 26.9 (C-11) , 25.4 (C-15). 20.7 (C-16). 17.7 (C-18).

Estra-1,3,5(10)-trien-3-yl acetate (**16).** White solid (0.46 g, 88%). M.p.: 109-110ºC (lit. 104 - 105ºC[29]).^{1}H NMR (500 MHz, $CDCl_3$):δ 7.32 – 7.28 (m, 1H), 6.84 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.79 (dd, *J* = 2.4, 1.1 Hz, 1H), 2.93-2.80 (m, 2H, H-6), 2.31 – 2.20 (m, 2H), 2.28 (s, 3H, H-20, CH_3), 1.11-1.96 (m, 13H), 0.74 (s, 3H, H-18).$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$):δ 170.0 (C-19), 148.4 (C-

3), 138.6 (C-5), 138.5 (C-10), 126.6 (C-1), 121.6 (C-4), 118.6 (C-2), 53.7 (C-14), 44.3 (C-9), 41.1 (C-13), 40.6 (C-17), 38.9 (C-12 and 8), 29.8 (C-6), 28.0 (C-7), 26.7 (C-11), 25.4 (C-15), 21.3 (C-20), 20.7 (C-16), 17.7 (C-18).

General procedure for the synthesis of (8*R*,9*S*,13*S*,14*S*)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolan]-3-ol (19) and (8*R*,9*S*,13*S*,14*S*)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolan]-3-yl acetate (20). To a suspension of estrone (0.33 g, 1.12mmol) in triethylorthoformate (3 ml, 18 mmol) and ethylene glycol (0.2 ml, 3.7 mmol), a catalytic amount of p-TsOH was added, and the mixture was gently heated at 70°C until the suspension became a clear solution (1 h). The warm reaction mixture was then poured into a saturated solution of sodium bicarbonate. A white solid separated from the reaction solution which was filtered off, washed with water and dried in the air. The acetylation reaction of compound **19** was carried out with acetic anhydride in pyridine according to the procedure previously described and, after recrystallization of the white solid residue from methanol, compound **20** was obtained.

(8*R*,9*S*,13*S*,14*S*)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolan]-3-ol (**19**). White solid (0.32 g; 90%). M.p.: 183 - 185ºC (lit. 180 - 181ºC[30]).^{1}H NMR (500 MHz, $CDCl_3$):δ 7.15 (d, *J*= 8.35 Hz, 1H, H-1), 6.62 (dd, *J*= 8.35 y 2.85 Hz, 1H, H-2), 6.56 (d, *J*= 2.71 Hz, 1H, H-4), 4.97 (s, 1H, OH-3), 3.99 - 3.87 (m, 4H, OCH_2CH_2O), 2.86 - 2.76 (m, 2H, H-6 and H-6'), 2.30 (m, 1H), 2.21 (td, *J* = 11.1 and 4.2 Hz, 1H), 2.03 (ddd, *J*=2.98, 11.65 and 14.27 Hz, 1H), 1.90-1.73 (m, 4H), 1.63 -1.23 (m, 6H), 0.88 (s, 3H, H-18).^{13}C{^{1}H} NMR (126 MHz,$CDCl_3$):δ 153.5 (C-3), 138.4 (C-5), 132.8 (C-10), 126.6 (C-1), 119.6 (C-17), 115.4 (C-4), 112.8 (C-2), 65.4 y 64.7 (OCH_2CH_2O), 49.5 (C-14), 46.3 (C-13), 43.7 (C-9), 39.2 (C-8), 34.4 (C-16), 30.9 (C-12), 29.8 (C-6), 27.1 (C-7), 26.3 (C-11), 22.5 (C-15), 14.5 (C-18).

(8*R*,9*S*,13*S*,14*S*)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolan]-3-yl acetate (**20**). White crystalline solid (0.30 g, 0.84 mmol, 83%), mp 250 -

251ºC (lit. 146 - 248ºC[29]). ^{1}H RMN (500 MHz, $CDCl_3$):δ 7.28 (dd, *J* = 8.5 Hz, 1.1 Hz, 1H, H-1), 6.84 (dd, *J* = 8.5, 2.6 Hz, 1H, H-2), 6.78 (d, *J* = 2.50 Hz, 1H, H-4), 3.99 – 3.86 (m, 4H, OCH_2CH_2O), 2.89 – 2.82 (m, 2H, H-6 y H-6'), 2.35 - 2.24 (ddt, *J* = 11.1, 4.4, 2.3 Hz, 2H), 2.28 (s, 3H, H-20), 2.03 (ddd, *J* = 14.1, 11.4, 2.9 Hz, 1H), 1.93 – 1.73 (m, 4H), 1.66 - 1.60 (m, 1H), 1.57 – 1.29 (m, 5H), 0.88 (d, *J* = 0.7 Hz, 3H, H-18). ^{13}C{^{1}H} RMN (126 MHz, $CDCl_3$):δ 167.0 (C-19), 148.5 (C-3), 138.4 (C-5), 138.2 (C-10), 126.5 (C-1), 121.6 (C-4), 119.5 (C-17), 118.6 (C-2), 65.4and 64.7 (OCH_2CH_2O), 49.5 (C-14), 46.2 (C-13), 43.9 (C-9), 38.8 (C-8), 34.3 (C-16), 30.8 (C-12), 29.8 (C-6), 26.9 (C-7), 26.1 (C-11), 22.5 (C-15), 21.3 (C-20), 14.4 (C-18).

Photoirradiations

General procedure for the irradiations of 3-acyl estrone derivatives. Stock solutions of esters (**1**, **2, 10, 16**and **20**; 0.106 mmol) were prepared in different organic media (250 mL). The photoirradiations of the esters were carried out as follow: i) analytical scale: a 2 mL aliquot of solution was placed in a stoppered 3 mL quartz cell and deaerated with argon for 20 min; ii) preparative scale: a 65 mL aliquot was placed in a stoppered 100 mL Erlenmeyer quartz flask and deaerated with argon for 30 min. The quartz cell as well as the Erlenmeyer quartz flask was placed in a home-made optical bench provided with eight lamps. In all the experiments the solutions of the esters were stirred during the irradiation process. Irradiations with λ_{exc}= 310 nm were carried out with four phosphorous coated lamps (HelioQuartz, each of 18 Watts) that give a nearly parallel beam at 310 nm. Irradiations with λ_{exc}= 254 nm were carried with eight germicide lamps (Philips, each of 20 Watts). The progress of the reaction was monitored by three different methods: (i) UV-visible spectroscopy; (ii) TLC [eluent: hexane-ethyl acetate (8: 2 v/v); spots were visualized with UV light (254 and 366 nm) and with cerium molybdate stain (Hanessian's stain)] and (iii) ^{1}HNMR spectroscopy. In order to isolate, purify and characterize the photoproducts, preparative photolysis (preparative scale) was conducted according to the following procedure. A solution of estrone derivative (0.106 mol) in cyclohexane (65 mL) was placed in a stoppered Erlenmeyer quartz flask and was irradiated with stirring under N_2 atmosphere employing the optical bench above described.

The irradiation time varied depending on the compound studied and the progress of the reaction was monitored by TLC and ^{1}HNMR spectroscopy. When total conversion of the starting material was reached, the photolyzed solution was evaporated carefully to dryness under vacuum. The yellowish solid residue obtained was worked up by silica gel column chromatography (eluent: hexane 100% followed by hexane-ethyl acetate mixtures). From the eluted fractions, the photoproducts were isolated and characterized by mean of physical and spectroscopic methods.

2-Acetyl-3-hydroxyestra-1,3,5(10)-trien-17-one (**3**)**.**White solid (0.018 g, 17%). M. p.: 162 - 163ºC (lit. 160-162ºC[31]).^{1}H NMR (500 MHz, $CDCl_3$):δ 12.04 (s, 1H, OH), 7.60 (d, *J* = 1.3 Hz, 1H, H-1), 6.70 (s, 1H, H-4), 2.97 – 2.83 (m, 2H, H-6), 2.60 (s, 3H, H-21), 2.52 (dd, *J* = 19.0, 8.7 Hz, 1H, H-16), 2.44 – 2.39 (m, 1H, H-11), 2.24 (td, *J* = 10.7, 4.3 Hz, 1H, H-11), 2.15 (dt, *J* = 18.9, 8.9 Hz, 1H, H-16'), 2.10 – 1.97 (m; 3H; H-12, H-7 and H-15), 1.66 – 1.41 (m; 6H; H-7', H-14, H-8, H-12', H-11' y H-15'), 0.92 (s, 3H, H-18). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$):δ 220,9 (C-17); 204,1 (C-20); 160,3 (C-3); 147,0 (C-10); 131,0 (C-5); 127,4 (C-1); 118,0 (C-2); 117,8 (C-4); 50,5 (C-14); 48,0 (C-13); 43,7 (C-9); 38,2 (C-8); 35,9 (C-16); 31,6 (C-12); 29,9 (C-6); 26,6 (C-21); 26,3 (C-7); 26,1 (C-11); 21,7 (C-15); 13.9 (C-18).

4-Acetyl-3-hydroxyestra-1,3,5(10)-trien-17-one (**4**). Pale yellow solid (0.026 g, 25%). M.p.: 195 - 196ºC. ^{1}H NMR (500 MHz, $CDCl_3$):δ 10.45 (s, 1H, H-19), 7.34 (d, *J*= 8.80 Hz, 1H, H-1), 6.81 (d, *J*= 8.80 Hz, 1H, H-2), 3.16 - 3.09 (m, 1H, H-6), 2.94 (ddd, *J* = 16.7, 5.6, 2.9 Hz, 1H, H-6'), 2.63 (s, 3H, H-21), 2.52 (dd, *J*= 18.90 y 9.16 Hz, 1H, H-16), 2.38 - 2.34 (m, 1H, H-11), 2.27 - 2.23 (m, 1H, H-9), 2.16 (dt, *J* = 19.0, 8.9 Hz, 1H, H-16'), 2.08-2.03 (m, 2H, H-7, H-15), 1.98 - 1.96 (m, 1H, H-12), 1.69 - 1.47 (m, 5H, H-14, H-15', H-8, H-12', H-11'), 1.44 - 1.36 (m, 1H, H-7'), 0.93 (s, 3H, H-18). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$):δ 220.7 (C-17), 206.8 (C-20), 157.8 (C-3), 136.8 (C-5), 131.8 (C-10), 131.7 (C-1), 123.8 (C-4), 115.9 (C-2), 50.4 (C-14), 48.2 (C-13), 44.7 (C-9), 37.9 (C-8), 36.0 (C-16), 33.5 (C-21), 31.8 (C-12), 30.1 (C-6), 26.4 (C-11), 26.3 (C-7), 21.6 (C-15), 14.1 (C-18). HMRS ESI $[M + H]^+$Calcd for $C_{20}H_{25}O_3^+$ 313.1798, found 313.1804.

(13β)-2-Acetyl-3-hydroxyestra-1,3,5(10)-trien-17-one (**6**)**.** White solid (0.015 g, 17%). M.p.: 160-163ºC. ^{1}H NMR (500 MHz, $CDCl_3$):δ 12.03 (s, 1H, OH), 7.58 (s, 1H, H-1), 6.68 (s, 1H, H-4), 2.89 – 2.80 (m, 2H, H-6), 2.59 (s, 3H, H-21), 2.43 – 2.21 (m, 4H, H-16, H-12, H-9 and H-11), 2.20 – 2.09 (m, 3H, H-16', H-7 and H-15), 1.98 – 1.92 (m, 1H, H-15'), 1.74 – 1.79 (m, 1H, H-14), 1.49 – 1.37 (m, 2H, H-12' and H-7'), 1.07 (s, 3H, H-18), 1.04 – 0.99 (m, 1H, H-11'), 0.95 – 0.89 (m, 1H, H-8). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$):δ 221.6 (C-17), 204.2 (C-20), 160.2 (C-3), 147.3 (C-10), 131.1 (C-5), 127.9 (C-1), 118.2 (C-2), 117.5 (C-4), 50.3 (C-13), 49.5 (C-14), 41.8 (C-9), 41.3 (C-8), 33.6 (C-16), 32.2 (C-12), 30.2 (C-6), 28.3 (C-7), 28.3 (C-11), 26.7 (C-21), 25.2 (C-18), 21.2 (C-15).HMRS ESI $[M + H]^+$Calcd for $C_{20}H_{25}O_3^+$ 313.1798, found 313.1806.

2-benzoyl-3-hydroxyestra-1,3,5(10)-trien-17-one (**7**). White solid (0.093 g, 62%). M.p.: 188-190ºC. ^{1}H RMN (500 MHz. $CDCl_3$):δ 11.87 (s, 1H, H-19), 7.67 (d, *J* = 6.96 Hz, 2H, H-22), 7.59 (dd, *J* = 7.49 and 7.35 Hz, 1H, H-24), 7.52 (dd, *J* = 7.77 and 7.35 Hz, 2H, H-23), 7.49 (s, 1H, H-1), 6.81 (sa, 1H, H-4), 3.00 - 2.89 (m, 2H, H-6), 2.50 (dd, *J*= 8.7, 19 Hz, 1H, H-16), 2.21 - 2.10 (m, 3H, H-9, H-16 and H-11), 2.08 - 2.00 (m, 2H, H-15 and H-7), 1.92 - 1.86 (m, 1H, H-12), 1.67 - 1.54 (m, 2H, H-15' and H-8), 1.51 - 1.38 (m, 4H, H-14, H-11', H-7' and H-12'), 0.90 (s, 3H, H-18). ^{13}C{^{1}H} RMN (126 MHz. $CDCl_3$):δ 220.7 (C-17), 201.3 (C-20), 161.2 (C-3), 146.9 (C-10), 138.3 (C-21), 131.9 (C-24), 130.8 (C-5), 130.6 (C-1), 129.2 (C-22), 128.5 (C-23), 117.8 (C-4), 117.4 (C-2), 50.5 (C-14), 48.0 (C-13), 43.7 (C-9), 38.3 (C-8), 35.9 (C-16), 31.5 (C-12), 30.0 (C-6), 26.3 (C-7), 25.8 (C-11), 21.7 (C-15), 13.9 (C-18).HMRS ESI $[M + H]^+$Calcd for $C_{25}H_{27}O_3^+$ 375.1955, found 375.1959.

4-Benzoyl-3-hydroxyestra-1,3,5(10)-trien-17-one **(8).** The NMR spectra showed a mixture of two conformers, which are expected to originate from de rotation of the benzoyl group. Pale yellowish solid (0.028 g, 19%).M.p.: 148 - 150ºC. The data belongs to the major conformer. ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.80 (d, *J*= 6.9 Hz, 1H, H-22), 7.59 (t, 1H, H-24), 7.47 (t. *J*=7.8 Hz, 1H, H-23), 7.31 (d, *J*=8.4 Hz, 1H, H-1), 6.82 (d, *J=8.5* Hz, 1H, H-2), 2.57 - 2.43 (m, 3H, H-6 and H-16), 2.41 - 2.33 (m, 1H, H-12), 2.23 (td, *J*= 4.0 and 10.4 Hz, 1H, H-9), 2.11 (dt, *J*= 8.8, 19.3 Hz, 1H, H-16), 2.03 - 1.92 (m, 2H, H-12 and H-15), 1.83 - 1.74 (m, 1H, H-7), 1.63 - 1.43 (m, 5H, H-14, H-11, H-

15, H-8 and H-12), 1.33 - 1.24 (m, 1H, H-7), 0.91 (s, 3H, H-18). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$):δ 221.2 (C-17), 200.3 (C-20), 153.5 (C-3), 138.8 (C-21), 136.0 (C-5), 133.5 (C-24), 132.7 (C-10), 129.4 (C-22), 128.9 (C-1), 128.8 (C-23), 124.9 (C-4), 114.5 (C-2), 50.6 (C-14), 48.2 (C-13), 44.1 (C-9), 37.9 (C-8), 35.9 (C-16), 31.7 (C-12), 28.4 (C-6), 26.1 (C-7), 25.9 (C-11), 21.7 (C-15), 14.0 (C-18).HMRS ESI $[M + H]^+$Calcd for $C_{25}H_{27}O_3^+$ 375.1955, found 375.1944.

(13β)-3-Hydroxyestra-1,3,5(10)-trien-17-one (**9**). White needles (0.018 g, 12%). M.p.:268 - 269°C (268 - 269°C[32]). ^{1}H NMR (500 MHz,):δ 7.15 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.64 (dd, *J* = 8.4, 2.8 Hz, 1H), 6.59 (d, *J* = 2.8 Hz, 1H), 2.79 (d, *J* = 8.2 Hz, 2H, H-6 and H-6'), 1.05 (s, 3H, H-18), 1.00 - 0.95 (m, 1H, H-11). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$):δ 222.1 (C-17), 153.6 (C-3), 138.4 (C-5), 132.1 (C-10), 127.2 (C-1), 115.2 (C-4), 113.1 (C-2), 50.3 (C-13), 49.5 (C-14), 41.6 (C-8), 41.6 (C-9), 33.7 (C-16), 32.2 (C-12), 30.3 (C-6), 28.4 (C-7 and C-11), 25.3 (C-18), 21.2 (C-15).

Compounds 3-[(4a*S*,10a*R*)-7-methoxy-2-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1-yl]propanal (**12**), 3-[(1*R*,2*R*,4a*S*,10a*S*)-7-methoxy-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl]propanal (**13**) and methyl 3-[(1*R*,2*R*,4a*S*,10a*S*)-7-methoxy-2-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl]propanoate (**14**) were obtained as an inseparable oily yellowish mixture. These compounds showed identical spectroscopic properties as those reported in the literature.[7]

Compound (**12**).^{1}H NMR (500 MHz, $CDCl_3$):δ 9.79 (t, *J* = 1.46 Hz, 1H, H-17), 7.23 (d, *J* = 8.56 Hz, 1H, H-1), 6.73 (dd, *J* = 8.51 and 2.85 Hz, 1H, H-2), 6.66 (d, *J* = 2.85 Hz, 1H, H-4), 3.79 (s, 3H, H-19), 2.94 – 2.90 (m, 2H, H-6), 2.51 – 2.44 (m, H-9), 2.07 – 1.98 (m, H-8), 1.7 (s, 3H, H-18). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 202.6 (C-17), 157.8 (C-3), 138.0 (C-5), 133.2 (C-10), 130.5 (C-14), 129.3 (C-13), 125.8 (C-1), 113.7 (C-4), 111.5 (C-2), 55.4 (C-19), 41.7 (C-8), 40.9 (C-9), 30.4 (C-6), 19.7 (C-18).

Compound (**13**).^{1}H NMR (500 MHz, $CDCl_3$):δ 9.83 (t, *J* = 1.42 Hz, 1H, H-17), 7.18 (d, *J* = 8.23 Hz, 1H, H-1), 6.71 (dd, *J* = 8.85 and 2.85 Hz, 1H, H-2), 6.62 (d, *J* = 6.62 Hz, 1H, H-4), 3.78 (s, 3H, H-19), 2.85 – 2.80 (m, 2H, H-6), 2.35 – 2.26 (m, H-9), 1.19 – 1.10 (m, H-8), 0.96 (d, *J* = 6.11 Hz,

3H, H-18). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 202.7 (C-17), 157.6 (C-3), 137.9 (C-5), 132.6 (C-10), 126.8 (C-1), 113.4 (C-4), 111.9 (C-2), 55.3 (C-19), 42.5 (C-9), 41.7 (C-8), 35.9 (C-12), 30.4 (C-6), 20.2 (C-18).

Compound (**14**).^{1}H NMR (500 MHz, $CDCl_3$):δ 7.20 (d, *J* = 8.81 Hz, 1H, H-1), 6.71 (dd, *J* = 8.85 and 2.85 Hz, 1H, H-2), 6.62 (d, *J* = 2.71 Hz, 1H, H-4), 3.78 (s, 3H, H-19), 3.68 (s, 3H, H-20), 2.85 – 2.80 (m, 2H, H-6), 2.33 – 2.17 (m, H-16), 2.35 – 2.26 (m, H-9), 1.98 – 1.86 (m, H-15), 1.36 – 1.31 (m, H-13), 1.19 – 1.10 (m, H-8), 1.04 – 1.00 (m, H-14), 0.96 (d, *J* = 6.11 Hz, 3H, H-18). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 174.8 (C-18), 157.5 (C-3), 138.1 (C-5), 133.0 (C-10), 126.7 (C-1), 113.4 (C-4), 111.8 (C-2), 55.3 (C-19), 51.7 (C-20), 47.4 (C-14), 43.1 (C-9), 42.7 (C-8), 35.8 (C-12), 34.6 (C-13), 31.3 (C-11), 30.5 (C-6), 29.4 (C-16), 26.5 (C-7), 23.6 (C-15), 20.5 (C-18).

(13α)-3-methoxyestra-1,3,5(10)-trien-17-one (**11**). White solid (0.042 g, 50%). M.p.: 125-127ºC (lit. 126-128ºC[7]). ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.21 – 7.16 (m, 1H, H-1), 6.70 (dd, *J* = 8.6, 2.8 Hz, 1H, H-2), 6.61 (d, *J* = 2.93 Hz, 1H, H-4), 3.76 (s, 3H, OCH_3), 2.84 – 2.82 (m, 2H, H-6), 2.41 – 2.08 (m, 7H, H-16, H-12, H-9, H-11, H-16', H-15 and H-7), 1.99 – 1.93 (m, 1H, H-15'), 1.75 (dd, *J* = 11.2, 5.21 Hz, 1H, H-14), 1.46 – 1.40 (m, 2H, H-12' and H-7'), 1.05 (s, 3H, H-18), 1.00 – 0.90 (m, 2H, H-8 and H-11'). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$):δ 221.8 (C-17), 157.6 (C-3), 138.2 (C-5), 132.1 (C-10), 127.0 (C-1), 113.7 (C-4), 111.9 (C-2), 55.4 (OCH_3), 50.3 (C-13), 49.5 (C-14), 41.7 (C-8), 41.6 (C-9), 33.6 (C-16), 32.2 (C-12), 30.5 (C-6), 28.5 (C-7), 28.4 (C-11), 25.3 (C-18), 21.2 (C-15).

1-[3-hydroxyestra-1,3,5(10)-trien-2-yl]ethanone (**17**). White solid (0.04 g, 46%). M.p.: 184 - 185ºC. ^{1}H NMR (500 MHz,$CDCl_3$):δ 12.03 (s, 1H, H-19), 7.62 (s, 1H, H-1), 6.69 (s, 1H, H-2), 2.88 - 2.84 (m, 2H, H-6), 2.60 (sa, 3H, H-21), 2.31 - 2.26 (m, 2H, H-11), 2.19 (td, *J* = 11.0, 4.3 Hz, 1H, H-9), 1.95 - 1.88 (m, 2H, H-17 and H-7), 1.80 - 1.61 (m, 3H, H-15, H-16 and H-16'), 1.57 - 1.50 (m, 2H, H-11' y H-12), 1.43 - 1.28 (m, 5H, H-15', H-7', H-8, H-17', H-12'), 1.18 - 1.12 (m, 1H, H-14), 0.77 (s, 3H, H-18). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$):δ 203.9 (C-20), 159.8 (C-3), 147.3 (C-5), 131.9 (C-10), 127.2 (C-1), 117.4 (C-4), 117.7 (C-2), 53.5 (C-14), 43.5 (C-9), 40.9 (C-13), 40.3 (C-12),

38.8 (C-8), 38.5 (C-17), 30.0 (C-6), 27.6 (C-7), 26.7 (C-11), 26.4 (C-21), 25.1 (C-15), 20.5 (C-16), 17.4 (C-18).HMRS ESI $[M + H]^+$Calcd for $C_{20}H_{27}O_2^+$ 299.2006, found 299.2003.

1-[3-hydroxyestra-1,3,5(10)-trien-4-yl]ethanone (**18**). Pale yellow needles (0.002 g, 32%). M.p.: 209 - 212ºC. ^{1}H NMR (500 MHz, $CDCl_3$):δ 10.66 (s, 1H, H-19), 7.37 (d, *J*= 8.68 Hz, 1H, H-1), 6.80 (d, *J*= 8.67 Hz, 1H, H-2), 3.14 - 3.07 (m, 1H, H-6), 2.91 - 2.86 (m, 1H, H-6'), 2.63 (sa, 3H, H-21), 2.25 - 2.19 (m, 2H, H-9 y H-11), 1.98 - 1.94 (m, 1H, H-7), 1.89 (dt, *J*= 12.64 y 2.79, 1H, H-17), 1.80- 1.63 (m, 3H, H-15, H-16 y H-16'), 1.54 - 1.47 (m, 2H, H-11' y H-12), 1.40 - 1.11 (m, 6H, H-15', H-7', H-8, H-17', H-12' and H-14), 0.77 (s, 3H, H-18). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$):δ206.8 (C-20), 157.9 (C-3), 137.1(C-5), 132.6 (C-10), 131.9 (C-1), 123.2 (C-4) ,115.5 (C-2), 53.3 (C-14), 44.6 (C-9), 41.1 (C-13), 40.3 (C-12), 38.8 (C-17), 38.5(C-8), 33.4 (C-21), 30.4 (C-6), 27.6 (C-7), 27.0 (C-11), 25.0 (C-15), 20.5 (C-16), 17.5 (C-18).HMRS ESI $[M + H]^+$Calcdfor $C_{20}H_{27}O_2^+$ 299.2006, found 299.2012.

1-[(8*R*,9*S*,13*S*,14*S*)-3-hydroxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolan]-2-yl]ethanone (**21**). White solid (0.02 g, 20%). M.p.: 198 - 200ºC.^{1}H NMR (500 MHz, $CDCl_3$):δ 12.03 (s, 1H, H-19), 7.60 (s, 1H, H-1), 6.68 (s, 1H, H-4), 3.99 – 3.88 (m, 4H, OCH_2CH_2O), 2.90 - 2.80 (m, 2H, H-6), 2.60 (s, 3H, H-21), 2.35 - 1.24 (13H), 0.89 (s, 3H, H-18). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$):δ 204.0 (C-20); 160.0 (C-3); 147,4 (C-10); 131,7 (C-5); 127,3 (C-1); 119.3 (C-17); 117,8 (C-2); 117.6 (C-4), 65.3 and 64.6 (OCH_2CH_2O), 49.4 (C-14); 46.0 (C-13); 43.2 (C-9); 38.8 (C-8); 34.2 (C-16); 30.5 (C-12); 29.9 (C-6); 26.6 (C-21); 26.5 (C-7); 26.1 (C-11); 22.4 (C-15); 14.3 (C-18). HMRS ESI $[M + H]^+$Calcd for $C_{22}H_{29}O_4^+$ 357.2060, found 357.2076.

1-[(8*R*,9*S*,13*S*,14*S*)-3-hydroxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolan]-4-yl]ethanone (**22**). White neddles(0.03 g, 27%). M.p.: 235-238ºC. ^{1}H NMR (500 MHz, $CDCl_3$):δ 10.57 (s, 1H, H-19), 7.35 (d, *J* = 8.8 Hz, 1H, H-1), 6.79 (d, *J* = 8.7 Hz, 1H, H-2), 3.99 – 3.89 (m, 4H, OCH_2CH_2O), 3.11 - 3.04 (m, 1H, H-6), 2.90 - 2.85 (m, 1H, H-6'), 2.62 (s, 3H, H-21), 2.29 - 2.20 (m, 2 H), 2.04 - 1.96

(m, 1H), 1.96 - 1.74 (m, 3H), 1.68 - 1.24 (m, 7H), 0.90 (s, 3H, H-18). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$):δ 207.0 (C-20), 157.9 (C-3), 137.2 (C-5), 131.9 (C-10), 123.6 (C-4), 119.4 (C-17), 115.7 (C-2), 65.4 and 64.7 (OCH_2CH_2O), 49.4 (C-14), 46.4 (C-13), 44.4 (C-9), 38.6 (C-8), 34.4 (C-16), 33.6 (C-12), 30.9 (C-6), 30.4 (C-21), 26.8 (C-7), 26.7 (C-11), 22.4 (C-15), 14.5 (C-18). HMRS ESI $[M + H]^+$Calcd for $C_{22}H_{29}O_4^+$ 357.2060, found 357.2049.

Preparation of the relative yield profiles. The relative yield profiles were constructed recording the ^{1}H-NMR spectra of the reaction mixture at different irradiation times after evaporation of the reaction solvent and then, dissolving the solid residue in deuterated chloroform. The aromatic protons of the steroid derivatives were chosen as the diagnostic signals and, after integration of these signals, the yields were calculated.

Supporting Information.

Copy of the 1D and 2D NMR spectra of starting compounds and photoproducts.UV-visible spectral change vs time of compound **16** and relative absorbance at 330 nm (A/A_∞) of formation of *ortho*-rearranged photoproducts (**17** and **18**) in MeOH. This material is available free of charge via the Internet at http://pubs.acs.org.

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Acknowledgement.

Partial support for this work from the University of Buenos Aires, Subsidio 20120160100124BA-Programa: 2017 – 2020. SMB and JAR are research members of CONICET. MIQ thanks CONICET for doctoral scholarship (Doctorate Program).

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