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VERSATILE PHOTOREARRANGEMENT OF PHOTOCYCLO-ADDUCTS FROM 5-FLUORO-1,3-DIMETHYLURACIL AND NAPHTHALENE

Kazue Ohkura,*[,a] Hiromichi Akizawa,[a] Mikiko Kudo,[a] Tetsuya Ishihara,[a] Nobuhiro Oshima,[a] and Koh-ichi Seki*[,b]

[a] Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan
E-mail: ohkura@hoku-iryo-u.ac.jp
[b] Central Institute of Radio Isotope Science, Hokkaido University, Kita-15, Nishi-7, Kita-ku, Sapporo 060-0815, Japan

Abstract – Direct UV-irradiation of 5-fluoro-1,3-dimethyluracil (5-FDMU) and naphthalene (**1**) with a 500 W high-pressure mercury lamp in a degassed Pyrex tube (λ > 300 nm) predominantly afforded benzopyrimidobarrelene derivative (**2**) through 1,4-addition, while irradiation in the presence of piperylene in singlet excited states preferentially afforded naphthocyclobuta- pyrimidine derivative (**3**) *via* 1,2-addition. Upon 254 nm light-irradiation of **2** gave rise to the formation of benzopyrimidosemibullvalene (**4**) in fair yields. The reaction pathway for the formation of **4** is reasonably explained in the terms of di-π-methane rearrangement. Adduct **3** was newly converted to the corresponding barrelene derivative (**2**) by long-wave-length irradiation in the presence of a triplet sensitizer.

INTRODUCTION

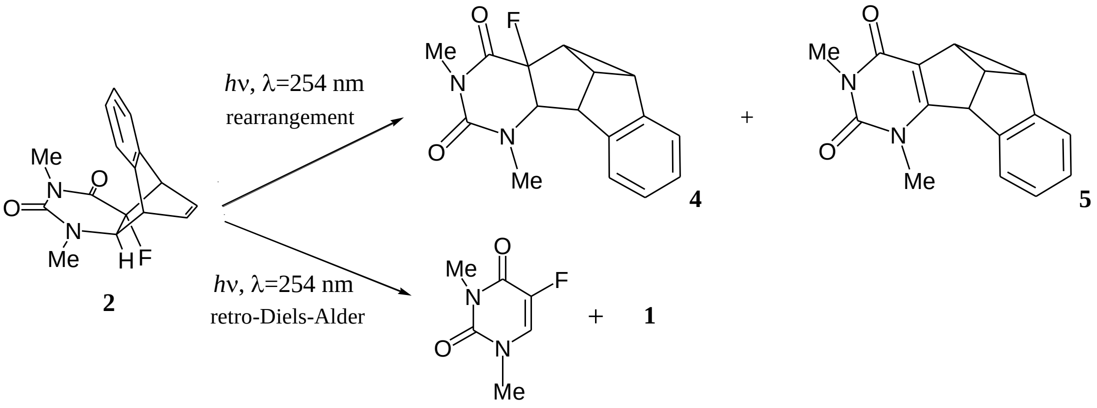
In recent years, significant attention has been paid to the photocycloaddition of naphthalenes with alkenes as a useful procedure for constructing certain unique ring systems by way of 1,2-,[1,2] 1,4-,[1,2] 1,3-,[3] 1,8-,[4] and [4 + 4] additions.[1,5] We previously reported that UV-irradiation of 5-fluoro-1,3-dimethyl- uracil (5-FDMU) and naphthalene (**1**) with a 500 W high-pressure mercury lamp in a degassed Pyrex tube (λ > 300 nm) predominantly afforded the 1,4-adduct, namely benzopyrimidobarrelene derivative (**2**) in high yield.[6] A time course study of the photoreaction of an acetonirile solution of 5-FDMU and **1** under the same conditions showed that the 1,2-cycloadduct, naphthocyclobutapyrimidine derivative (**3**) is formed as the major product at the initial stage, which however, is quite labile to the UV-light used, to revert rapidly back to 5-FDMU and **1**, while the 1,4-adduct (**2**) was produced competitively with **3**, though less effectively but insensitive to the light, to accumulate in the reaction mixture as the irradiation time is prolonged.[7] The addition of the triplet quencher piperylene to the reaction mixture of **1** and 5-FDMU dramatically changed the mode of cycloaddition, resulting in the preferential formation of **3** through 1,2-addition.[8] Thus, 1,4- and 1,2- adducts of the pyrimidine ring and naphthalene have been synthesized mode-selectively in fair yields upon long-wave-length irradiation by a high-pressure mercury lamp with a Pyrex filter (λ > 300 nm). Furthermore, we have obtained 1,3-cycloadducts, semibullvalene derivatives (**4**), by the UV-irradiation with a low-pressure mercury lamp (λ = 254 nm). The semibullvalenes were found to be secondary products derived from initially formed 1,4-adducts under UV-irradiation, although the precise reaction mechanism remained unclear.[9] Thus, we have hitherto demonstrated a mode selective synthesis of three types of cycloadducts, 1,2-, 1,3-, *albeit* formally, and 1,4-adducts, by controlling the reaction conditions appropriately.

Although versatile photorearrangements of 1,4-adducts and 1,2-adducts of aromatic hydrocarbons with alkenes have extensively been explored,[10-12] little is known about the photochemical behavior of heteroaromatic-fused barrelenes except pyrazinobarrelenes and benzoquinoxalinobarrelenes.[13] Hence, our attention was focused to elucidate an aspect of the reciprocal valence isomerization of the adducts of 5-FDMU with naphthalene. In the present paper we describe the feature of the mutual conversion of the cycloadducts between 5-FDMU and **1**.

RESULTS AND DISCUSSION

Photoisomerization of benzopyrimidobarrelene (2)

First, we examined photochemical behavior of 1,4-adduct (**2**). Upon UV-irradiation with a high-pressure



Scheme 1

mercury lamp (λ > 300 nm), starting barrelene **2** was recovered unchanged, while irradiation of **2** in cyclohexane for 5 min with 254 nm light from a 60 W low-pressure mercury lamp gave rise to the formation of semibullvalene (**4**) in fair yields (40%), together with a trace amount of novel dehydrofluorinated semibullvalene derivative (**5**), and cyclo-reversionary products, 5-FDMU and **1**, in 20% yield (Scheme 1).

Time course experiments of the present photolysis with ^{1}H-NMR spectroscopy showed that prompt formation of **4** occurred first, while the formation of **5** was barely detectable at the initial stage (Figure 1).

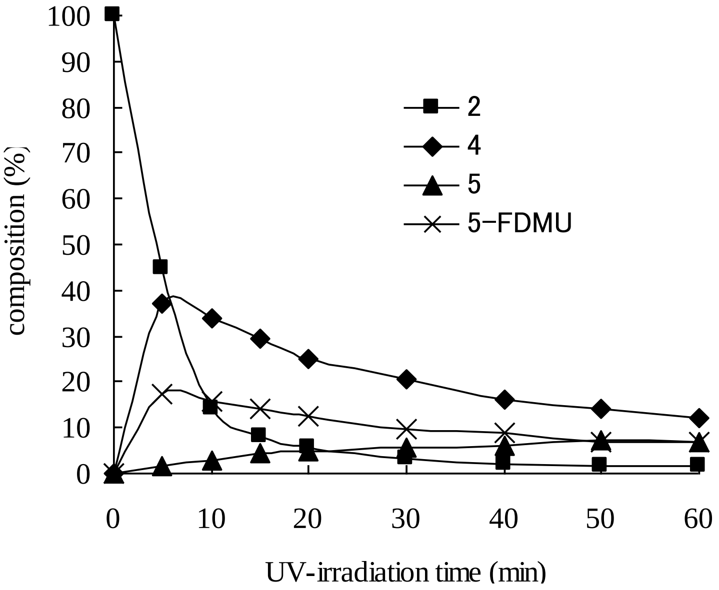
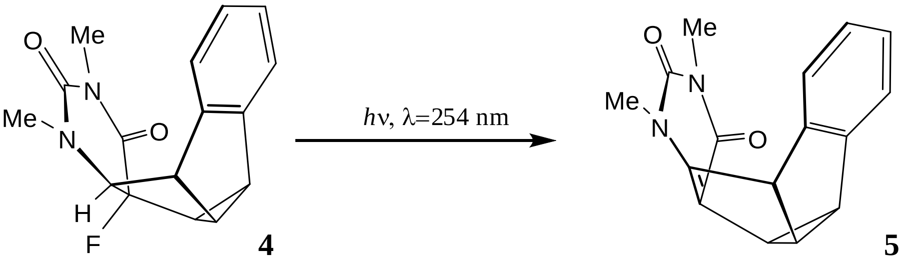


Figure 1

The formation of **4** reached a maximum at 5 min. With the decrease of **4**, formation of **5** rose. These results indicate that semibullvalene (**4**) may be converted to the dehydrofluorinated derivative (**5**) during the irradiation.

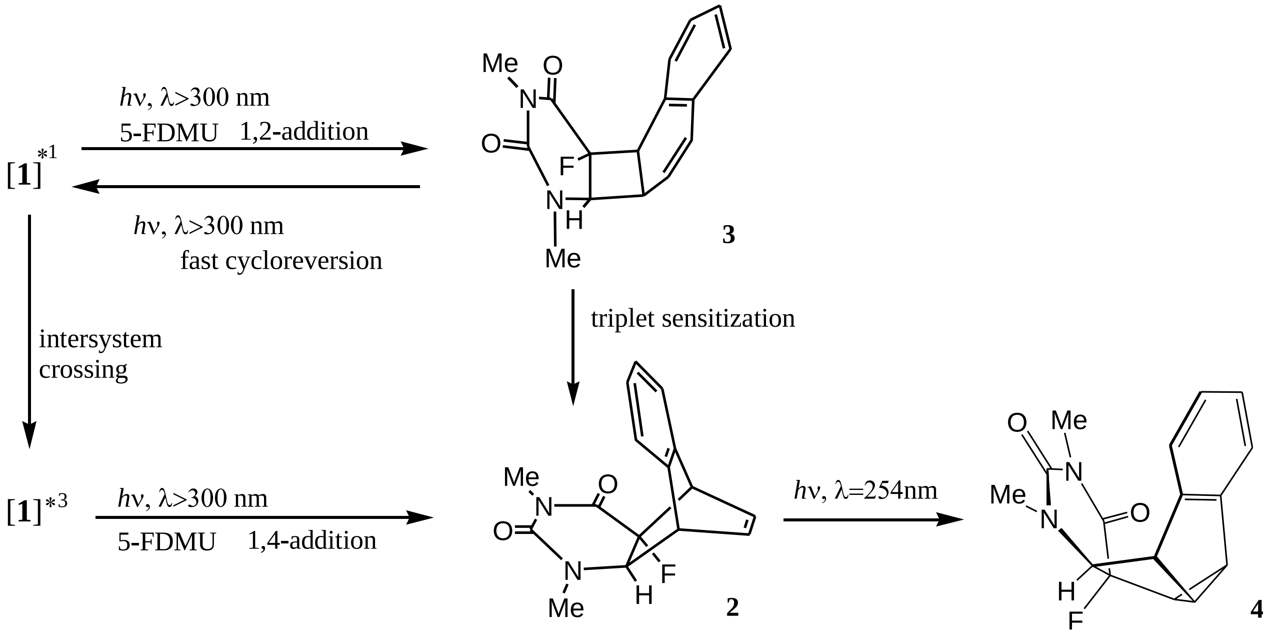
Indeed **4** gave semibullvalene **5** as a major product upon irradiation in cyclohexane with 254 nm light for 30 min (Scheme 2).



Scheme 2

Photoisomerization of naphthocyclobutapyrimidine (3)

We then examined the photochemical behavior of 1,2-adduct (**3**). Direct irradiation of **3** with a high pressure mercury lamp (10 min) only restored the starting materials, 5-FDMU and **1**, in high efficiency (63%). By contrast, the UV-irradiation of **3** in the presence of a triplet sensitizer, benzophenone, gave rise to the formation of benzopyrimidobarrelene (**2**) (10%), in competition with cyclo-reversion to the original **1** and 5-FDMU (55%) (Scheme 3).

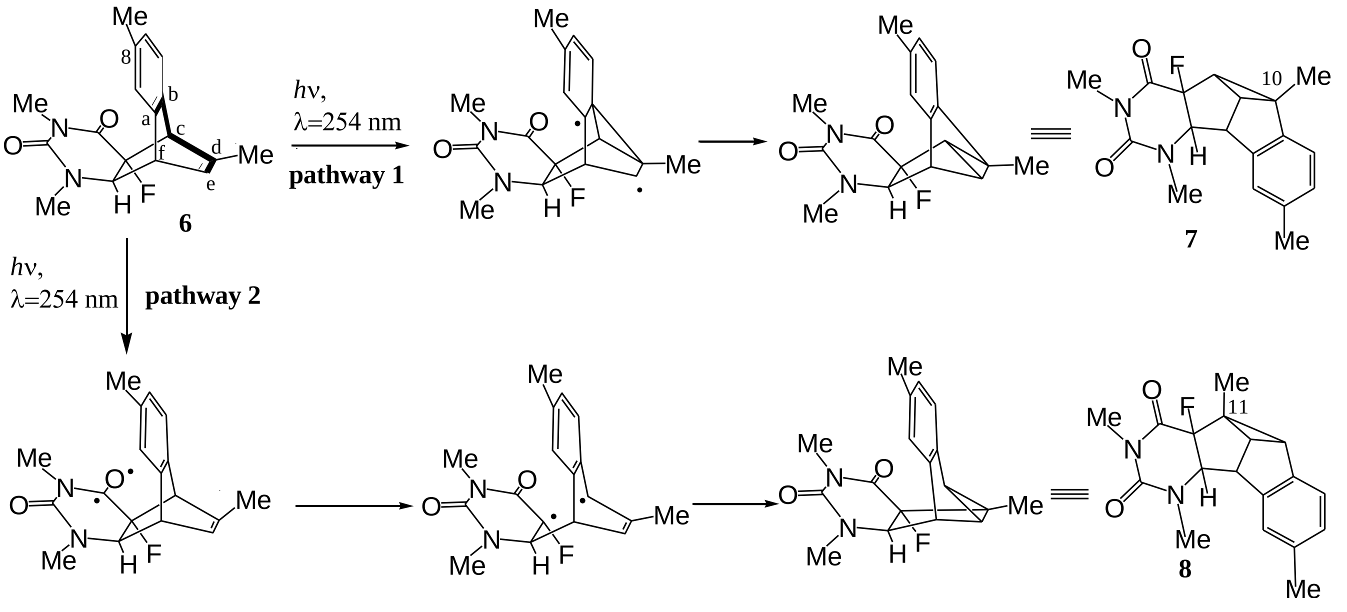


Scheme 3

The transformation from 1,2-adduct (**3**) to 1,4-adduct (**2**) can be explained by a mechanism involving biradical intermediate in the excited triplet state, as proposed by J. Aretz *et al*.[14]

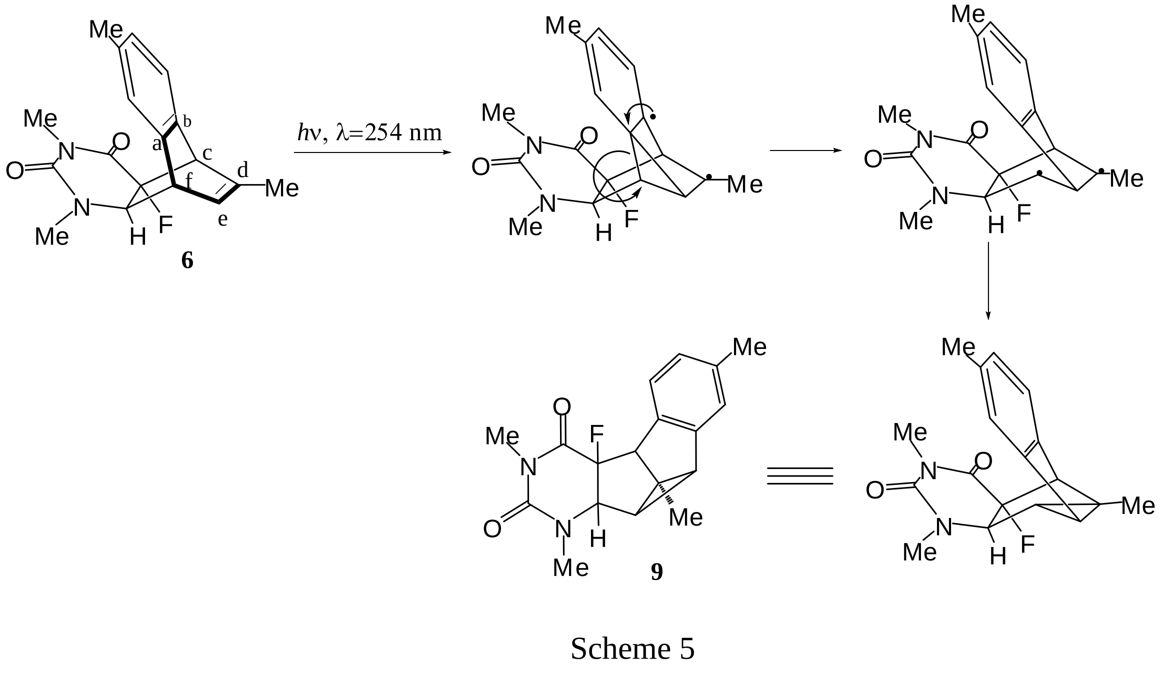
Mechanistic studies for the formation of semibullvarene (4) from benzopyrimidobarrelene (2)

The formation of semibullvarene **4** from **2** can be accounted either in terms of di-π-methane rearrangement[10] (pathway 1, participating atoms/bonds are denoted as a-b-c-d-e in Scheme 4), or by a mechanism involving a biradical intermediate (pathway 2 in Scheme 4). It would be readily clarified by carrying out the photoreaction with 8,12-dimethylbenzopyrimidobarrelene (**6**), whereby either 11a-fluoro-4a,10,11-trihydro-2,4,7,10-tetramethyl-5,10,11-metheno-*5H*-benzo[5,6]cyclohepta[1,2-*d*]pyrimidine-1,3-dione (**7**) *via* di-π-methane rearrangement, or 11a-fluoro-4a,10,11-trihydro-2,4,7,10-tetramethyl-5,10,11-metheno-*5H*-benzo[5,6]cyclohepta[1,2-*d*]pyrimidine-1,3-dione (**8**) through a biradical intermediate should be produced.



Scheme 4

UV-Irradiation of **6** with a low-pressure mercury lamp resulted in the formation of **7** (18%) yield, clearly demonstrating that di-π-methane rearrangement is involved in the present photo-transformation. In this reaction a novel type semibullvalene, 4a-Fluoro-10,11,11a-trihydro-1,3,8,12-tetramethyl-5,10,11-metheno-*5H*-benzo[4,5]cyclohepta[1,2-*d*]pyrimidine-1,3-dione (**9**) was also produced through di-π-methane rearrangement shown in Scheme 5 (participating atoms/bonds are denoted as b-a-f-e-d) (14%). Although methyl groups on barrelene derivative may be influential on radical reactions, these results



Scheme 5

exhibit significant participation of di-π-methane rearrangement in the reaction pathway for the formation of **4**.

CONCLUSION

The present study clearly demonstrates the reciprocal photochemical valence isomerization of the cycloadducts of 5-FDMU and naphthalene. 1,4-adduct **2** which is intact to a long-wave-length light ($\lambda > 300$ nm), is readily converted into benzopyrimidosemibullvalene (**4**) with a short-wave-length light ($\lambda = 254$ nm). By contrast, 1,2-cycloadduct (**3**) is sensible to the light from a high-pressure mercury lamp ($\lambda > 300$ nm), to restore 5-FDMU and naphthalene through cyclo-reversion, whereas UV-irradiation with a high-pressure mercury lamp in the presence of a triplet sensitizer effected valence isomerization of **3** into **2**. Thus, 1,2-, 1,3-, and 1,4-cycloadducts of 5-FDMU with naphthalene are shown to be produced mode-selectively.

From the viewpoint of photochemistry of aromatic- and heteroaromatic-fused cycloadducts, it is worthy of note that adducts **2** and **3** photo-isomerize with the fluoride atom remaining intact at the original position, while the photolysis of semibullvalene (**4**) gives pyrimidine-fused semibullvalene (**5**) *via* dehydrofluorination.

EXPERIMENTAL

NMR spectra were measured with a JEOL JNM-EA500 (500 MHz) spectrometer, and ^{1}H-NMR chemical shifts were given on the δ (ppm) scale based on those of the solvent signals. MS spectra and high-resolution MS (HRMS) spectra were recorded with a LEOL JMS-HX110 (FAB). HPLC was conducted on a Shim-pac PREP-Sil (H) (25 cm x 20 mm *i. d.*) (silica gel), using a LC-10A apparatus (Shimadzu, Kyoto) with monitoring at 254 nm. UV-Irradiation was carried out externally with a 60 W low-pressure lamp (Eiko-sha, Osaka) in a quartz tube under argon ($\lambda = 254$ nm) or a 500 W high-pressure mercury lamp (Eiko-sha, Osaka) in a degassed Pyrex tube ($\lambda > 300$ nm) on a merry-go-round apparatus. Yields were determined using ^{1}H-NMR spectroscopy with p-dinitrobenzene as an internal standard. Benzopyrimidobarrelene (**2**) was synthesized by the photoreaction of 5-FDMU and **1** in cyclohexane solution with a high-pressure mercury lamp ($\lambda > 300$ nm).[6] Naphthocyclobutapyrimidine (**3**) was prepared by the similar photoreaction of 5-FDMU and **1** in the presence of piperylene.[7]

Photolysis of 2 in cyclohexane ----- A solution (0.051 mmol) of **2** in cyclohexane (70 mL) was put portionwise (10 mL each) into 7 quartz tubes, and irradiated externally with a 60 W low-pressure lamp under an argon atmosphere at room temperature. The reaction mixture was concentrated *in vacuo*, and the residual oil was subjected to HPLC with 30% EtOAc in hexane.

11a-Fluoro-4a,10,11-trihydro-2,4-dimethyl-5,10,11-metheno-*5H*-benzo[5,6]cyclohepta[1,2-*d*]pyrimidine-1,3-dione(4): ^{1}H-NMR(methanol-d_4) δ:2.47(3H, s, N^2-CH$_3$), 2.48(1H, ddd, *J*= 6.3, 8.0, 18.3Hz, H-11), 2.74 (1H, dd, *J*= 6.3, 8.0 Hz, H-10), 3.07 (1H, ddd, *J*= 6.3, 6.3, 6.3 Hz, H-12), 3.14 (3H, s, N^4-CH$_3$), 4.07 (1H,ddd, *J*= 1.7, 6.3, 6.9 Hz, H-5), 4.44 (1H,dd, *J*= 6.9, 30.4 Hz, H-4a), 6.85 (1H, d, *J*= 7.5 Hz, H-6), 7.02 (1H, ddd, *J*= 1.2, 7.5, 7.5 Hz, H-7), 7.12 (1H, ddd, *J*= 1.2, 7.5, 7.5 Hz, H-8), 7.22 (1H, d, *J*=7.5 Hz, H-9). NOE: H-11with H-10 (19.7%), H-12 (3.6%); H-10 with H-12 (3.9%), H-9 (1.9%); H-12 with H-5 (3.6%), H-10 (2.4%); N^4-CH$_3$ with H-4a (2.3%), H-5(1.3%), H-6(1.1%); H-5 with H-4a (4.6%), H-6 (2.0%), H-12 (4.3%), N^4- CH$_3$ (2.0%). FAB-MS (*m/z*): [M + H]$^+$ 287. HRFAB-MS (*m/z*): [M + H]$^+$ Calcd for $C_{16}H_{16}FN_2O_2$, 287.1196; Found, 287.1204.

10,11-Dihydro-2,4-dimethyl-5,10,11-metheno-*5H*-benzo[5,6]cyclohepta[1,2-*d*]pyrimidine-1,3-dione (5):^{1}H-NMR(acetone-d_6) δ:3.03 (1H, t, *J*= 6.9Hz, H-11), 3.08 (3H, s, N^2-CH$_3$), 3.15 (1H, dd, *J*= 6.3, 6.9Hz, H-10), 3.44 (1H, ddd, *J*= 6.3, 6.9, 6.9Hz, H-12) ,3.58 (3H, s, N^4-CH$_3$), 4.71 (1H, d, *J*= 6.9 Hz, H-5), 7.11 (1H, dt, *J*= 1.2,7.5 Hz, H-7), 7.18 (1H, dt, *J*= 1.2, 7.5 Hz, H-8), 7.38 (1H, d, *J*= 7.5Hz, H-6), 7.40 (1H, d, *J*= 7.5Hz, H-9). NOE: H-11 with H-10 (1.0%), H-12 (1.8%). FAB-MS (*m/z*): [M + H]$^+$ 267.HRFAB-MS (*m/z*): [M + H]$^+$ Calcd for $C_{16}H_{15}N_2O_2$, 267.1133; Found, 267.1129.

Photolysis of 4 in cyclohexane ----- A solution (0.034 mmol) of **4** in cyclohexane (70 mL) was UV irradiated under the same conditions described above to afford **5** (28%) together with unreacted **4** (37%).

Photolysis of 6 in cyclohexane ----- A solution (0.027 mmol) of **2** in cyclohexane (50 mL) was put portionwise (10 mL each) into 5 quartz tubes, and irradiated externally with a 60 W low-pressure lamp under an argon atmosphere for 5 min at room temperature. The reaction mixture was concentrated *in vacuo*, and the residual oil was subjected to HPLC with 1% EtOAc in CH_2Cl_2 to give **7**(18%) and **9** (14%), together with unreacted **6** (26%).

11a-Fluoro-4a,10,11-trihydro-2,4,7,10-tetramethyl-5,10,11-metheno-*5H*-benzo[5,6]cyclohepta[1,2-*d*]-pyrimidine-1,3-dione (7): ^{1}H-NMR(CDCl$_3$) δ:1.54 (3H, s, C^{10}-CH3), 2.25 (3H, s, C^7-CH$_3$), 2.38 (1H, dd, *J*= 6.3, 18.9Hz, H-11), 2.53 (3H, s, N^2-CH$_3$), 2.72 (1H, dd, *J*= 5.2, 6.3 Hz, H-12), 3.14 (3H, s, N^4-CH$_3$), 3.87(1H, dd, *J*= 5.2, 6.3 Hz, H-5), 4.16 (1H, dd, *J*= 6.3, 29.8 Hz, H-4a), 6.60 (1H, s, H-6), 6.98 (1H, d, *J*= 7.5 Hz, H-8), 7.08 (1H, d, *J*= 8.0Hz, H-9). NOE: C^{10}-CH$_3$ with H-11(1.6%), H-12 (1.0%), H-9 (1.4%);

H-4a with N^4-CH_3 (5.3%), H-5 (6.3%), H-12 (1.3%); H-5 with H-12 (5.6%), N^4-CH_3(2.8%), H-4a (7.1%), H-6 (3.1%); N^4-CH_3 with H-5 (1.4%), H-4a (2.4%), H-6 (1.6%). FAB-MS (*m/z*): $[M + H]^+$ 315. HRFAB-MS (*m/z*): $[M + H]^+$ Calcd for $C_{18}H_{20}FN_2O_2$, 315.1508; Found, 315.1510.

4a-Fluoro-10,11,11a-trihydro-1,3,8,12--tetramethyl-5,10,11-metheno-*5H*-benzo[4,5]cyclohepta[1,2-*d*]-pyrimidine-1,3-dione (9): ^{1}H-NMR($CDCl_3$) δ : 1.67 (3H, s, C^{12}-CH_3), 2.13 (1H, dd, *J*= 6.3, 7.5 Hz, H-11) 2.26 (3H, s, C^8-CH_3), 2.41 (1H, d, *J*=7.5 Hz, H-10), 2.74 (3H, s, N^1-CH_3), 2.95 (3H, s, N^3-CH_3), 3.81(1H, dd, *J*= 2.9, 12.6 Hz, H-5), 4.28 (1H, ddd, *J*= 2.9, 6.3, 26.9 Hz, H-11a), 6.68 (1H, d, *J*= 7.5Hz, H-6), 6.81(1H, d, *J*=7.5Hz, H-7), 7.04 (1H, s, H-9). NOE: C^{12}-CH_3 with H-11 (1.6%), H-10 (1.6%), H-5 (2.3%); H-11 with C^{12}-CH_3 (2.4%), H-10 (7.3%), N^1-CH_3 (2.8%), H-11a (8.8%); C^8-CH_3 with H-7 (2.1%), H-9 (2.2%); H-10 with C^{12}-CH_3(1.6%), H-11(7.3%), N^1-CH_3 (1.2%), H-9 (3.7%); H-5 with C^{12}-CH_3 (2.4%), H-6 (3.2%); H-11a with H-11(7.4%), N^1-CH_3(3.5%); H-6 with N^3-CH_3 (1.6%), H-5 (3.9%), H-7 (7.7%); H-9 with C^8-CH_3 (4.6%), H-10 (3.8%), N^1-CH_3 (1.4%). FAB-MS (*m/z*): $[M + H]^+$ 315. HRFAB-MS (*m/z*): $[M + H]^+$ Calcd for $C_{18}H_{20}FN_2O_2$, 315.1508; Found, 315.1512.

Photosensitization of 3 ----- An acetonirile solution of **3** (0.025 M) was irradiated in the presence of benzophenone (0. 83 M) with a 500 W high-pressure mercury lamp in a degassed Pyrex tube to give **2** (10%) together with 5-FDMU (55%).

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