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Regioselective Aza-annulation to a Heterocyclic Ketene Aminal: A New Route to Ethyl 1-Oxo-2,3-dihydropyrido-[1,2-a]-(5*H*)-perimidine-4-carboxylates

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ABSTRACT: *Ethyl (1H-perimidin-2-yl)acetate* **1** *reacts with various acrylic acid chlorides* **3** *to afford new ethyl 1-oxo-2,3-dihydropyrido-[1,2-a]-(5H)-perimidine-4-carboxylates* **4** *by regioselective aza-annulation with the appropriate base. The* ^{1}H, ^{13}C *NMR spectrum of some representative annulated perimidines* **4** *and* C_β*-acylated products* **7** *are discussed.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9:523–528, 1998

INTRODUCTION

Ketene aminals, members of the enamine family, are versatile intermediates [1] in organic synthesis. Ethyl (1*H*-perimidin-2-yl)acetate **1** [2] simultaneously exhibits the distinct properties of heteroatomic systems with an excess of and a deficiency of π-electrons [2]. Due to the electron-donating ability of nitrogen atoms and the electron-withdrawing ability of the carboxylate group, the double bond $C_\alpha = C_\beta$ of **1′** is highly polarized as a consequence of a "push-pull" effect, and the electron density on C_β is increased [4], leading to greater nucleophilicity of carbon C_β when compared to nitrogen [5].

Our interest in this field has been focused on the synthetic use of amphoteric perimidine **1** toward annulation from α and β-dielectrophiles [6], and also in tandem conjuguate carbon addition-intermolecular hetero Diels–Alder reactions [7]. Encouraged by the potential biological activity [8] of the 2-perimidylidene moiety of the fused heterocycles **2** (Figure 1) as chemotherapeutic agents (in-vitro anti-HIV activity [9]), we decided to explore the reactivity of ethyl (1*H*-perimidin-2-yl)acetate **1** toward aza-annulation with α, β-unsaturated acid chlorides **3**.

The aza-annulation [10] of **1** is mechanistically interesting because the perimidine unit **1** is an ambident nucleophile that can react at the N-1 or C_β position, and the α, β-unsaturated acid chloride **3** is an ambident electrophile [11] that can react at positions 1′ or 3′ (Scheme 1). In principle, two regioisomeric products **4** and **5** could result from this reaction.

We report here the results of this aza-annulation study of perimidine **1**. Preparative procedures including full characterization of new ethyl 1-oxo-2,3-dihydropyrido-[1,2-a]-(5*H*)-perimidine-4-carboxylates **4** are presented here.

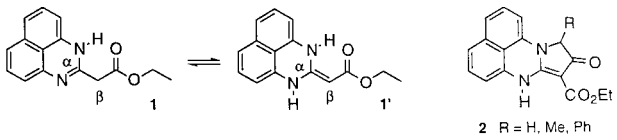

FIGURE 1 Fused heterocycles **2**.

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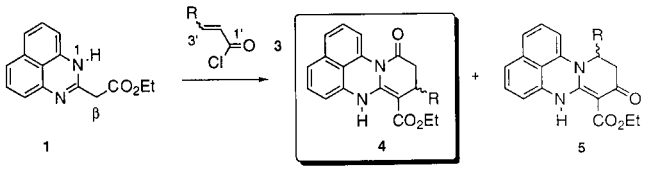


SCHEME 1

RESULTS AND DISCUSSION

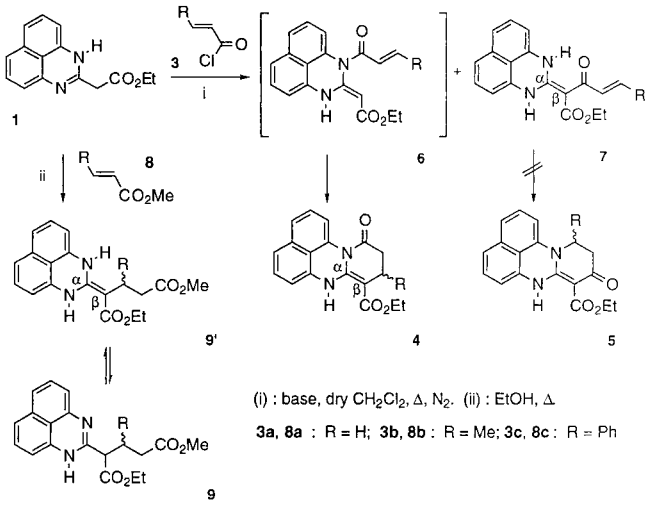
In order to check the reactivity of ethyl (1*H*-perimidin-2-yl)acetate **1**, acryloyl chloride **3a** (R = H), *trans*-crotonyl chloride **3b** (R = Me), and *trans*-cinnamoyl chloride **3c** (R = Ph) were used to determine the effects of olefin substitution in the aza-annulation reaction.

When perimidine **1** was treated with acryloyl chloride **3a** in dry methylene chloride with added Et_3N, a 42:58 ratio of **4a**:**7a** was obtained (Scheme 2). The same reaction conditions were conducted successively with *trans*-crotonyl chloride **3b** and *trans*-cinnamoyl chloride **3c**. From **3b**, a 92:8 ratio of **4b**:**7b** was observed, and optimum aza-annulation afforded **4c** in quantitative yield by reaction of **1** with **3c**.

From the standard samples of **4a/7a**, **4b/7b**, and **4c/7c**, systematic studies were performed to determine the effect of acyl species **3(a–c)** and bases (Et_3N, iPr_2NEt, 1,4-diazabicyclo[2,2,2]octane) on this product distribution (Table 1).

The reactivity of the acyl group and of the base were found to have a significant effect on product selectivity. The aza-annulation efficiency with acryloyl chloride **3a** was better with diisopropylethylamine (95:5 ratio of **4a**:**7a**), and the C-acylation reaction became competitive with DABCO. Increasing the bulkiness of the β-position of the unsaturated acid chloride **3** from hydrogen atom (**3a**) to phenyl group (**3c**) make the N-acylation and C_β-conjugate addition process more favorable using Et_3N and DABCO than the C_β-acylation reaction. Similarly, the C_β-acylation reactions increased with the bulkiness of the β-substituent of **3** when iPr_2NEt was used, for example, the reaction of **1** with *trans*-cinnamoyl chloride **3c** produced a 22:78 ratio of **4c**:**7c**.

A characteristic feature of the C_β-acylated products **7(a–c)** is that no product **5** corresponding to an intramolecular C-conjugate addition reaction was detected. The conjugation of the ester and carbonyl groups with the C_α/C_β double bond and the formation of the intramolecular hydrogen bonds both stabilize the product **7** in the enediamine form. This can be explained by the *peri*-amidine resonance [12] and the rotation barrier around the C_α/C_β bond being considerably reduced [13].



SCHEME 2

TABLE 1 Reaction of Ethyl (1*H*-Perimidin-2-yl)acetate **1** with Acrylic Acid Chlorides **3(a–c)** Derivatives

		Base used[a] and ratio of 4/7[b]			*(%) Isolated Yield of[c]*	
3	*R*	*Et_3N*	*iPr_2NEt*	*DABCO[d]*	*Product* **4**	*Product* **7**
3a	H	42:58	95:5	22:78	64	50
3b	Me	92:8	54:46	49:51	68	51
3c	Ph	100:0	22:78	100:0	64	50

[a]Reaction time: 4 hours at 41°C with dry CH_2Cl_2 as solvent.
[b]The ratios of **4/7** were determined by ^1H NMR spectroscopy in $CDCl_3$ solution with TMS as internal reference.
[c]Isolated yield of major product.
[d]DABCO: 1,4-diazabicyclo[2,2,2]octane.

Analysis of the reaction products (Table 1) shows that the choice of the base controls the N-acylation versus annulation pathway. In general, the options can be divided into two divergent routes, those that acylate first at nitrogen (intermediate **6**) and those that C-acylate (compound **7**). In the second case, the intramolecular addition was not favored in the enediamine tautomer **7**. When the amide-bond in **6** is formed, this intermediate can be converted to **4** by intramolecular C_β-conjugate addition that was simultaneously dependent on the steric hindrance at the β-position of **3** and on the base reactivity.

The assigned structures of compounds **4(a–c)** and **7(a–c)** were substantiated by the ^1H, ^{13}C NMR spectroscopic data and MS analyses. For **4a**, the shift of the NH signal (δ_{NH} 11.70) accounts for an intramolecular hydrogen bond. We have also found that the C_α/C_β bond revealed a strong polarization (**4a**:δ_{C_2} 147.8 and $\delta_{C\beta}$ 80.9) that is attributed to the intracyclic "push-pull" double-bond structure. The presence of an amide carbonyl carbon signal (δ_{CO} 170.7)

is in good agreement with N-acylation. From *trans*-crotonyl chloride **3b**, the corresponding C_β-acylated compound **7b** exhibits a *trans*-structure (**7b**: ^3J = 15 Hz) for the vinylidene segment [14]. Moreover, the downfield shift of NH signals is due to intramolecular hydrogen bond [15] formation in the ene-diamine form **7(a–c)** (**7a,b**: δ_{NH} 11.88 and 14.28; **7c**: δ_{NH} 11.92 and 14.40).

In the same way, we have extended the C_β-conjugate addition reactions of various methyl propenoates **8(a–c)** to ethyl (1*H*-perimidin-2-yl)acetate **1** (Scheme 2). Experimentally, only the reaction of **8a** (R = H) and **1** in refluxing dry ethanol afforded the C_β-addition product **9a** in 75% yield after purification by chromatography on silica gel (Table 2).

The structure of compound **9a** was established by the ^{1}H, ^{13}C NMR spectroscopic data and MS analysis. According to the ^{1}H NMR data in $CDCl_3$, it is noteworthy that the C_β-conjugate addition product is a mixture of tautomers **9a** and **9a′** (ratio **9a/9a′**:1/1). In the ^{1}H NMR spectrum, the signal due to H_β of **9a** is a triplet at δ 3.42 (^3J = 7.5 Hz) and the ^{1}H coupled ^{13}C NMR spectrum showed the presence of the C_β-doublet of **9a** centered at δ 50.2 (^3J = 137 Hz). Moreover, the upfield shift of C_β of **9a′** (δ 76.2) indicates a high electron density on this β-carbon, and this is located at δ 152.7. In fact, the double-bond C_α/C_β is also highly polarized as a consequence of a "push-pull" effect. Our initial aim was to approach the annulation of **9a**, but no cyclocondensation has been observed [15], and also no retro C_β-addition reaction has been detected [7].

CONCLUSION

The reaction of acrylic acid chlorides **3(a–c)** derivatives with ethyl (1*H*-perimidin-2-yl)acetate **1** has led to efficient heterocyclic aza-annulation. A study of substituent effects of **3** and the reactivity of base has provided information on the scope and the regiochemistry of this N,C-cyclocondensation. The annulated compounds **4(a–c)** were prepared in a single step by an N-acylation/intramolecular C_β-conjugate addition. This study was also extended to the regioselective synthesis of C_β-acylated products **7(a–c)**. The potential chemotherapeutic activity of ethyl 1-oxo-2,3-dihydropyrido-[1,2-a]-(5*H*)-perimidine-4-carboxylate **4(a–c)** will be examined. Further extensive research based on this methodology is underway in our laboratory.

TABLE 2 Reaction of Ethyl (1*H*-Perimidin-2-yl)acetate **1** with Methyl Propenoate **8(a–c)** Derivatives

Reagent	*R*	*Reaction Time*	*Reagent*	*Yield (%)*[a]
8a	H	12 h	**9a**	(98) 75
8b	Me	72 h	**9b**	—[b]
8c	C_6H_5	150 h	**9c**	—[b]

[a]Yield to crude product estimated by ^{1}H NMR (TMS as internal reference) and isolated yield after purification.
[b]No reaction.

EXPERIMENTAL SECTION

General

Thin-layer chromatography (TLC) was accomplished on 0.2 mm precoated plates of silica gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm) or with a fluorescence indicator. For preparative chromatography, silica gel 60 F-254 Merck (230–240 Mesh ASTM) was used. Melting points were determined on a Kofler melting-point apparatus and are uncorrected.

IR spectra were taken with a PERKIN-ELMER 157G spectrometer. ^{1}H NMR spectra were recorded on BRUKER ARX 200P (200 MHz) and BRUKER AC 300P (300 MHz) spectrometers, and ^{13}C NMR spectra, on a BRUKER AC 300P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane (TMS) as an internal standard. Unless otherwise stated, δ values refer to singlet absorptions. Data are given in the following order: δ value, multiplicity (s, singulet; d, doublet; t, triplet, q, quartet; m, multiplet; br, broad), number of protons; coupling constants J are given in Hertz. The mass spectra (HRMS) were taken on a VARIAN MAT 311 instrument at an ionizing potential of 70 eV in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Campus de Beaulieu, Rennes).

Acetonitrile and methylene chloride were distilled over calcium chloride, after having been allowed to stand over the drying agent overnight, and stored over molecular sieves (3 Å). Absolute ethanol was distilled over magnesium after having been allowed to stand overnight and stored over molecular sieves (3 Å). Solvents were evaporated with a Buchi rotary evaporator. Triethylamine and diisopropylethylamine were refluxed over calcium hydride and then distilled before use.

All reagents were purchased from Acros, Aldrich Chimie and used without further purification. Ethyl (1*H*-perimidin-2-yl)acetate **1** was synthetized according to our previous method [2] from commercial 1,8-diaminonaphthalene and ethyl 2-(ethoxycarbonyl)acetimidate hydrochloride prepared by the method of McElvain and Schroeder [16].

General Procedure for the Preparation of Ethyl 1-oxo-2,3-Dihydropyrido-[1,2-a]-(5H)-perimidine-4-carboxylates **4(a–c)** *and C_β-Acylated Compounds* **7(a–c)**. In a 100 mL two-necked flask with exclusion of moisture ($CaCl_2$ tube) were placed ethyl (1*H*-perimidin-2-yl)acetate **1** (0.25 g, 0.98 mmol), the appropriate base (1.08 mmol), and dry methylene chloride (5 mL). The suspension was heated at 41°C until complete dissolution with vigorous stirring. Then, a solution of acyl chloride **2** (1.08 mmol) in 3 mL of dry CH_2Cl_2 was added dropwise under nitrogen during 0.5 hour. The resulting mixture was heated at 41°C for 4 hours (monitored by TLC over 0.2 mm precoated plates of silica gel 60 F-254, Merck). The solution was allowed to cool to room temperature, and 30 mL of methylene chloride was added to the reaction mixture. The organic solution was treated with saturated Na_2CO_3 (2 × 10 mL), with water (3 × 15 mL), dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated in vacuo to give a viscous oil that crystallized on standing. Purification by gravity chromatography on silica gel 60 F-254 (Merck) provided two fractions (excepted for compound **4b**). The first fraction gave the desired compound **4**, and the second fraction gave the C_β-acylated compounds **7** that were recrystallized from acetone. Compounds **4(a–c)** and **7(a–c)** were characterized by ^1H, ^{13}C NMR, IR, and HRMS analyses.

Ethyl 1-oxo-2,3-Dihydropyrido-[1,2-a]-(5H)-perimidine-4-carboxylate (**4a**). The crude product **4a** (R = H) was obtained from ethyl (1*H*-perimidin-2-yl)acetate **1** (0.25 g, 0.98 mmol), freshly distilled N,N-diisoproprylethylamine (0.14 g, 1.08 mmol), and acryloyl chloride **3a** (0.098 g, 1.08 mmol). After work-up as described in the standard procedure, purification by chromatography (eluent = CH_2Cl_2/MeCN:19/1, *Rf* = 0.88) gave pure **4a** as brown crystals in 64% yield, mp = 126–128°C; IR (nujol) 1690, 1650, 1605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.32 (t, 3H, *J* = 7.1 Hz); 2.69 (dm, 4H, H-2 and H-3); 4.21 (q, 2H, *J* = 7.1 Hz); 6.58 (t, 1H, H-6); 7.19 (d, 2H, H-8, H-9); 7.36 (m, 2H, H-7, H-10); 8.12 (d, 1H, H-11); 11.70 (br s, 1H, NH, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.5 (qt, *J* = 127, 2.5 Hz); 17.3 (tt, *J* = 135, 3.9 Hz, C-2, C-3); 34.3 (tt, *J* = 131, 5.7 Hz, C-2, C-3); 59.9 (tq, *J* = 147, 4.4 Hz); 80.9 (sm, C-4); 106.6 (dm, *J* = 160 Hz, C-6); 114.7 (sm, C-11b); 116.9 (d, C-11); 119.8–123.5 (dm, C-8, C-9); 126.7–126.8 (d, C-7, C-10); 129.6–131.1–133.4 (s, C-5a, C-8a, C-11a); 147.8 (s, C-4a); 169.6 (s, CO); 170.7 (s, C-1). HRMS, *m/z* (%): 308 (M^+, 18), 262 (M-EtOH, 100), 234 (M-HCO_2Et, 9). (Found: M^+, 308.1151. $C_{18}H_{16}N_2O_3$ requires *M*, 308.1160).

Ethyl 3-Methyl-1-oxo-2,3-dihydropyrido-[1,2-a]-(5H)-perimidine-4-carboxylate (**4b**). The crude product **4b** (R = Me) was obtained from ethyl (1*H*-perimidin-2-yl)acetate **1** (0.25 g, 0.98 mmol), freshly distilled triethylamine (0.11 g, 1.08 mmol), and *trans*-crotonyl chloride **3b** (0.098 g, 1.08 mmol). After work-up, purification by chromatography (eluent = CH_2Cl_2, *Rf* = 0.69) gave pure **4b** as brown crystals in 68% yield, mp = 122–124°C; IR (nujol) 1700, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.18 (d, 3H, *J* = 7.1 Hz, CH_3–CH); 1.33 (t, 3H, *J* = 7.1 Hz); 2.68 (dd, 1H, *J* = 16, 2.1 Hz, ABX system of H-2); 2.90 (dd, 1H, *J* = 16, 6 Hz, ABX system of H-2); 3.13 (m, 1H, H-3); 4.24 (q, 2H, *J* = 7.2 Hz); 6.65 (t, 1H, H-6); 7.24 (d, 2H, H-8 , H-9); 7.43 (m, 2H, H-7, H-10); 8.34 (d, 1H, H-11); 11.83 (br s, 1H, NH, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.5 (qt, *J* = 126, 2.5 Hz); 18.8 (qm, *J* = 127 Hz, $\underline{C}H_3$–CH); 23.8 (dq, *J* = 137, 3.1 Hz, C-3); 41.1 (tm, *J* = 127 Hz, C-2); 59.9 (tq, *J* = 147, 4.4 Hz); 86.0 (sm, C-4); 106.7 (dm, *J* = 160 Hz, C-6); 114.6 (sm, C-11b); 116.4 (ddd, *J* = 168, 7.8, 3 Hz, C-11); 119.8–123.5 (dm, C-8, C-9); 126.9 (d, C-7, C-10); 129.9–131.3–133.5 (s, C-5a, C-8a, C-11a); 147.0 (s, C-4a); 169.7 (s, CO); 170.2 (s, C-1). HRMS, *m/z* (%): 322 (M^+, 54), 276 (M-EtOH, 100), 248 (M-HCO_2Et, 15), 234 (M-CH_3CO_2Et, 59), 206 (M-C_2H_3-CH_3, 93), 69 (C_3H_5-CO^+, 16). (Found: M^+, 322.1319. $C_{19}H_{18}N_2O_3$ requires *M*, 322.1317.)

Ethyl 1-oxo-3-Phenyl-2,3-dihydropyrido-[1,2-a]-(5H)-perimidine-4-carboxylate (**4c**). The crude product **4c** (R = Ph) was obtained from ethyl (1*H*-perimidin-2-yl)acetate **1** (0.25 g, 0.98 mmol), freshly distilled triethylamine (0.11 g, 1.08 mmol), and *trans*-cinnamoyl chloride **3c** (0.18 g, 1.08 mmol). After work-up, purification by chromatography (eluent = CH_2Cl_2, *Rf* = 0.84) gave pure **4c** as brown crystals in 64% yield, mp = 148–150°C; IR (nujol) 1750, 1670, 1640, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.23 (t, 3H, *J* = 7.1 Hz); 3.09 (d, 2H, *J* = 6.5 Hz, H-2); 4.18 (q, 2H, *J* = 7.1 Hz); 4.30 (dd, 1H, H-3); 6.62 (t, 1H, H-6); 7.23 (m, 9H, Ar); 7.40 (d, 1H, Ar); 8.15 (d, 1H, H-11); 12.03 (br s, 1H, NH, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.5 (qt, *J* = 127, 2.5 Hz); 33.9 (dt, *J* = 136 Hz, C-3); 41.1 (td, *J* = 129, 5.4 Hz, C-2); 60.2 (tq, *J* = 147, 4.4 Hz); 83.9 (s, C-4); 107.1 (d, *J* = 161 Hz, C-6); 114.9 (s, C-11b); 116.8 (dd, *J* = 168 Hz, C-11); 120.1–123.7 (dm, *J* = 163 Hz, C-8, C-9); 126.8–126.9 (d, C-2′, C-3′); 127.1 (d, *J* = 163 Hz, C-7, C-10); 128.8 (d, C-4′); 129.6–131.2–133.5 (s, C-5a, C-8a, C-11a); 142.2 (st, *J* = 4.4 Hz, C_{ipso}); 148.3 (s, C-4a); 169.4 (s, CO); 169.9 (s, C-1). HRMS, *m/z* (%): 384 (M^+, 29), 338 (M-EtOH, 40), 310 (M-HCO_2Et, 6), 131 (C_6H_5-$C_2H_2^+$, 100). (Found: M^+, 384.1474. $C_{24}H_{20}N_2O_3$ requires *M*, 384.1457.)

Ethyl 3-Oxo-2-(1H-Perimidin-2-ylidene)-pent-4-enoate (**7a**). The crude product **7a** (R = H) was obtained from ethyl (1*H*-perimidin-2-yl)acetate **1** (0.25 g, 0.98 mmol), 1,4-diazabicyclo[2,2,2]octane (0.12 g, 1.08 mmol), and acryloyl chloride **3a** (0.098 g, 1.08 mmol). After work-up, purification by chromatography (eluent = CH_2Cl_2, *Rf* = 0.6) and recrystallization from acetone gave pure **7a** as brown crystals in 50% yield, mp = 156–158°C; IR (nujol) 1700, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.36 (t, 3H, *J* = 7.1 Hz); 4.25 (q, 2H, *J* = 7.2 Hz); 5.48 (dd, 1H, *J* = 10.3, 2.1 Hz, H-5); 6.13 (dd, 1H, *J* = 17, 2.1 Hz, H-5); 6.37–6.44 (2xd, 2H, *J* = 6.7 Hz, H-4′, H-9′); 7.11 (m, 5H, H-4, H-5′, H-6′, H-7′, H-8′); 11.88 (br s, 1H, NH); 14.28 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3 (qt, *J* = 127, 2.5 Hz); 60.4 (tq, *J* = 148, 4.8 Hz); 87.6 (st, C-2); 106.0–106.7 (2xdd, *J* = 161 Hz, C-4′, C-9′); 118.0 (sm, C-9b′); 120.0–120.2 (dm, *J* = 161 Hz, C-6′, C-7′); 122.9 (t, *J* = 159 Hz, C-5); 127.9–128.1 (2xd, *J* = 161 Hz, C-5′, C-8′); 133.1–134.4 (s, C-3a′, C-9a′, C-6a′); 138.1 (dd, *J* = 161, 4.6 Hz, C-4); 155.7 (s, C-2′); 170.5 (s, C-1); 189.1 (s, C-3). HRMS, *m/z* (%): 308 (M^+, 18), 262 (M-EtOH, 100), 234 (M-HCO_2Et, 9), 206 (M-$C_2H_3CO_2Et$, 22), 55 (CH_3-CO^+, 18). (Found: M^+, 308.1179. $C_{18}H_{16}N_2O_3$ requires *M*, 308.1161.)

Ethyl (4E) 3-Oxo-2-(1H-Perimidin-2-ylidene)-hex-4-enoate (**7b**). The crude product **7b** (R = Me) was obtained from ethyl (1*H*-perimidin-2-yl)acetate **1** (0.25 g, 0.98 mmol), 1,4-diazabicyclo[2,2,2]octane (0.12 g, 1.08 mmol), and *trans*-crotonyl chloride **3b** (0.098 g, 1.08 mmol). After work-up, purification by chromatography (eluent = CH_2Cl_2, *Rf* = 0.69) and recrystallization from acetone gave **7b** in 51% yield (together with **4b**: 4%), mp = 156–158°C; IR (nujol) 1700, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34 (t, 3H, *J* = 7.1 Hz); 1.89 (d, 3H, *J* = 6.5 Hz, H-6); 4.25 (q, 2H, *J* = 7.1 Hz); 6.42–6.48 (2xd, 2H, *J* = 6.7 Hz, H-4′, H-9′); 6.73 (m, 1H, H-5); 6.90 (d, 1H, J_{trans} = 15 Hz, H-4); 7.13 (m, 4H, H-5′, H-6′, H-7′, H-8′); 11.88 (br s, 1H, NH); 14.28 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.4 (qt, *J* = 125, 2.5 Hz); 18.3 (qm, *J* = 130 Hz, C-6); 60.3 (tq, *J* = 147, 4.5 Hz); 87.2 (sm, C-2); 105.9 (dm, *J* = 160 Hz, C-5); 106.0–106.5 (dd, *J* = 161 Hz, C-9′); 117.1 (sm, C-9b′); 119.8–119.9 (dm, *J* = 161 Hz, C-6′, C-7′); 127.9–128.1 (d, *J* = 160 Hz, C-5′, C-8′); 133.0–133.2–134.5 (s, C-3a′, C-6a′, C-9a′); 136.9 (d, *J* = 160 Hz, C-4); 155.8 (s, C-2′); 170.7 (s, C-1); 189.3 (s, C-3). HRMS, *m/z*: 317.1319 found ($C_{18}H_{16}N_2O_3$ requires: 317.1317).

Ethyl (4E) 3-Oxo-5-Phenyl-2-(1H-perimidin-2-ylidene)-pent-4-enoate (**7c**). The crude product **7c** (R = Ph) was obtained from ethyl (1*H*-perimidin-2-yl)acetate **1** (0.25 g, 0.98 mmol), freshly distilled N,N-diisoproprylethylamine (0.14 g, 1.08 mmol), and *trans*-cinnamoyl chloride **7c** (0.18 g, 1.08 mmol). After work-up, purification by chromatography (eluent = CH_2Cl_2, *Rf* = 0.76) and recrystallization from acetone gave pure **7c** as brown crystals in 50% yield, mp = 138–140°C: IR (nujol) 1710, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.37 (t, 3H, *J* = 7.1 Hz); 4.28 (q, 2H, *J* = 7.1 Hz); 6.39–6.46 (2xd, 2H, *J* = 7.1 Hz, H-4′, H-9′); 7.04–7.62 (m, 13H, H-5′, H-6′, H-7′, H-8′, Ar, H-4, H-5); 11.92 (br s, 1H, NH); 14.40 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.7 (qt, *J* = 127, 2.5 Hz); 60.5 (tq, *J* = 148, 4.3 Hz); 88.2 (st, *J* = 3.3 Hz, C-2); 106.0–106.7 (2xdd, *J* = 162, 8.2 Hz, C-4′, C-9′, C-4); 118.1 (s, C-9b′); 120.0–120.2 (2xdm, *J* = 162 Hz, C-6′, C-7′); 127.8–128.2–128.8–128.9–129.2 (Ar); 133.3–134.5–136.1 (3xs, C-3a′, C-6a′, C-9a, C_{ipso}); 138.1 (dq, *J* = 157, 3.4 Hz, C-5); 155.8 (s, C-2′); 170.7 (s, CO); 188.6 (st, C-3). HRMS, *m/z* (%): 384 (M^+, 20), 338 (M-EtOH, 100), 131 (Ph-$C_2H_2CO^+$, 13). (Found: M^+, 384.1439. $C_{24}H_{20}N_2O_3$ requires *M*, 384.1474.)

Ethyl 4-Methoxycarbonyl-2-(1H-perimidin-2-yl)butenoate (**9a**). A mixture of ethyl (1*H*-perimidin-2-yl)acetate **1** (0.5 g, 1.97 mmol), methyl acrylate **8a** (0.18 g, 2.17 mmol), and dry ethyl alcohol (7 mL) was refluxed for 12 hours with vigourous stirring and then cooled. The solvent was removed in vacuo, and the crude residue (98% yield) was purified by gravity chromatography on silica gel 60 F-254 (Merck) using CH_2Cl_2/MeCN:9/1 as eluent. Concentration of the desired fraction (*Rf* = 0.41) gave the C_β-addition product **9a** as a nearly pure oil (75% yield) that crystallized on standing, mp = 110–112°C; IR (nujol) 1720, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.23 (2xt, 6H, *J* = 7.1 Hz); 2.30 (t, 2H, *J* = 7.2 Hz); 2.51 (d, 2H, *J* = 7.2 Hz); 2.60 (s, 4H); 3.42 (t, 1H, *J* = 7.5 Hz); 3.60–3.77 (2xt, 3H, *J* = 7 Hz, Ar); 4.20 (2xq, 4H, *J* = 7 Hz); 6.47–6.59 (2xd, 3H, *J* = 7 Hz, Ar); 7.14 (m, 9H); 9.00 (br s, 1H, NH); 12.00 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1–14.7 (2xqt, *J* = 127, 2.5 Hz); 19.3 (tm, *J* = 127 Hz); 26.8 (tm, *J* = 124 Hz); 31.3 (tt, *J* = 123 Hz); 34.6 (tt, *J* = 129 Hz); 50.2 (dt, *J* = 137 Hz, C-2 of **9a**); 51.8–52.7 (2xq, *J* = 147 Hz); 59.0–62.0 (2xtq, *J* = 148, 4.3 Hz); 76.2 (s, C-2 of **9a′**); 104.7 (d, C-4, C-9 of **9a** and **9a′**); 114.5 (sm, C-9b of **9a**); 118.3–118.6 (2xdm, *J* = 160 Hz, C-5, C-8 of **9a** and **9a′**); 122.0 (s, C-9b of **9a′**); 127.8–128.1 (2xd, *J* = 160 Hz, C-6, C-7 of **9a** and **9a′**); 134.3–134.4 (2xs, C-3a, C-9a of **9a**, C-3a of **9a′**); 135.10 (sd, *J* = 8.8 Hz, C-9a of **9a′**); 135.3 (sm, C-6a of **9a** and **9a′**); 150.0–152.7 (2xs, C-2 of **9a** and **9a′**); 170.8 (CO); 172.1 (CO); 172.9 (CO); 177.3

(CO). HRMS, m/z = 340.1424 found (calculated for $C_{19}H_{20}N_2O_4$: 340.1424), M^+.

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