Facile Synthesis of 4-Alkoxycarbonylisoquinoline-1,3-diones and 5-Alkoxycarbonyl-2-benzazepine-1,3-diones *via* a Mild Alkaline Cyclization

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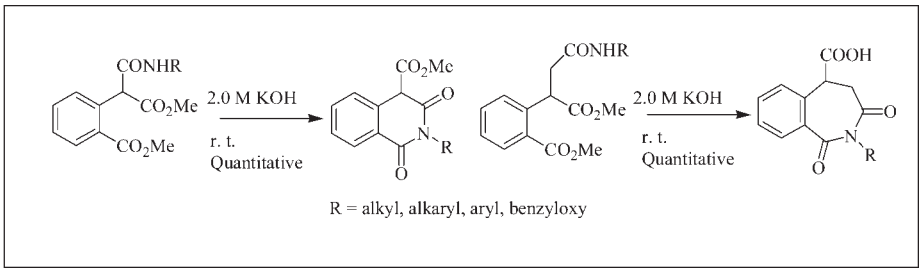

A series of 4-methoxycarbonylisoquinoline-1,3-diones was obtained from homophthalic acid in four steps. The key step was the quantitative and rapid alkaline cyclization of 2-methoxycarbonyl-2-(2-methoxycarbonylphenyl) acetamides. Homologation easily afforded in the same conditions 5-carboxy-2-benzazepine-1,3-dione.

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INTRODUCTION

4-Substituted isoquinoline-1,3-dione framework may serve as the backbone for the production of several series of biologically active compounds, mainly in the field of diabetes (aldose reductase inhibitors) [1], inflammation [2] (cycloxygenase [3] and lipoxygenase [4] inhibitors), herbicides, and plant growth regulators [5]. Our current research program is devoted to the evaluation of 2-hydroxyisoquinoline-1,3-diones as potential HIV-1 integrase and/or ribonuclease H inhibitors. For that purpose, we needed to develop a facile and efficient route to 4-alkoxycarbonyl-2-benzyloxyquinoline-1,3-diones as precursor of the lead compounds.

Two routes were possible (Scheme 1). The first one consists in synthesizing the 4-unsubstituted isoquinoline-1,3-dione by reaction of a primary amine with homophthalic anhydride, acid or diester (Scheme 1; route a) [1,3,5]. Then functionalization at position 4 is usually performed by reacting the isoquinoline-1,3-dione with a cyanoformate [1], a chloroformate [5], an acylchloride [3], or a sulfonylchloride [3] in presence of a base (pyridine, $LiN(SiMe_3)_2$, NaH or DBU) [1,3,5]. In our hands, the reaction of 2-benzyloxyisoquinoline-1,3-dione with methyl chloroformate in presence of a base (LDA or NaH) allowed us to isolate the desired product only in poor yields, because of a low reactivity and a degradation of the quinoline ring. Alternatively, ortho-halogenated benzoic acids can be converted to a dimethylmalonate derivative by the Hurtley reaction and the treatment with the appropriate amine gives 4-alkoxycarbonyl-isoquinoline-1,3-diones after activation with thionyl chloride (Scheme 1; route b) [1,6,7].

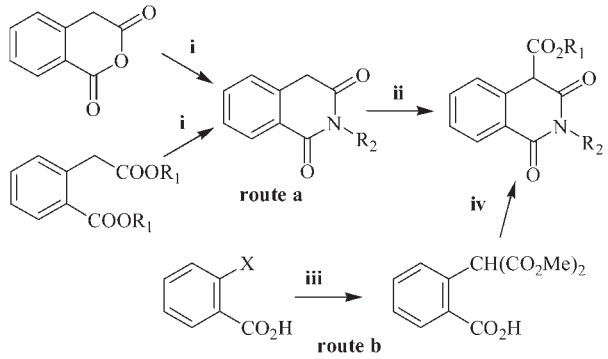
Once again, we could not obtain satisfactorily the cyclized product by this method. We also noticed a third possibility, which consists in treating quinone monoacetals with diethylmalonate in presence of KOtBu. However, to date, only one example using this method has been reported [8].

These failures led us to modify route b by activating a carboxylic acid function of the malonate derivative instead of activating the benzoic acid function. We report herein synthetic studies on this novel four step procedure (Scheme 2). A series of 4-methoxycarbonyl-isoquinoline-1,3-diones variously substituted at the nitrogen atom was obtained (Table 1).

RESULTS AND DISCUSSION

Homophthalic acid **1** was quantitatively esterified with methylic alcohol. The anion of the homophthalic diester **2** obtained by treatment with LDA reacted with carbon dioxide according to Lazer *et al.* [9] to yield the methyl 2-(2-methoxycarbonylphenyl) malonate monoester **3** in 62% yield. Using activation with the BOP reagent [10], the corresponding amides **4a-h** were synthesized with

Scheme 1. Reagents and conditions: (i) R_2NH_2, DMF, or xylenes; (ii) $ClCOOR_1$, pyridine, or $CNCOOR_1$, $LiN(SiMe_3)_2$, THF; (iii) NaH, CuBr, $CH_2(COOMe)_2$; (iv) $SOCl_2$ then R_2NH_2, THF.



several alkyl, alkylaryl, aryl, benzyloxy amines, and glycine in satisfactory yields (52–85%). The cyclization was easily achieved using 2.5*M* potassium hydroxide in aqueous methanol at room temperature for 5 min. This reaction was quantitative and the 2-substituted-4-methoxycarbonylisoquinoline-1,3-diones **5a-h** were isolated as variable mixtures of keto (0–50%) and enol (50–100%) forms. When the nitrogen atom was substituted by an ethoxycarbonylmethyl group (**4f**, Table 1), hydrolysis of this ethyl ester function occurred during the cyclization process whereas the residual methyl ester of the malonate derivative was conserved. Thus compound **5f** is substituted at position 2 by a carboxymethyl group, which could be variously functionalized (by a peptidic structure for example). Conversely, the carbon-chlorine bond in compound **4g** (Table 1) was found to be resistant to the basic conditions of cyclization.

This easy alkaline cyclization process led us to investigate the possible synthesis of homologous derivatives. For this purpose, homophthalic dimethyl ester **2** was first alkylated with allyl bromide in the presence of LDA (Scheme 3) to give **6**. The allylic oxidation with potassium periodate and potassium permanganate afforded methyl 2-(carboxymethyl)-2-(2-methoxycarbonylphenyl) ethanoate **7** in 63% yield. Using benzyloxy-

Scheme 2

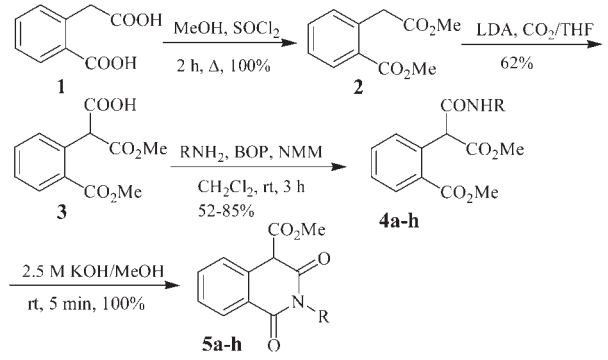


Table 1

Structures of the synthesized 2-substituted-4-methoxycarbonylisoquinoline-1,3-diones **5a-h**.

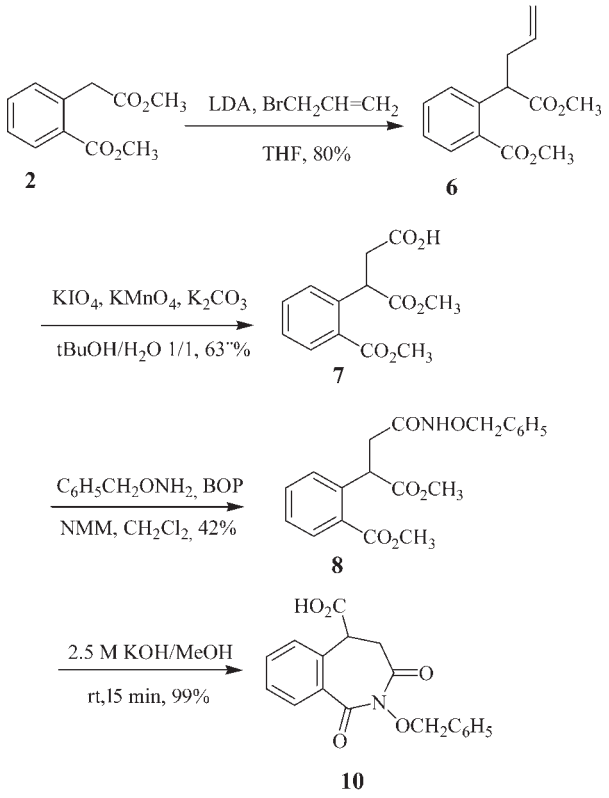
Entry	R	Yield (%)[a]
5a	$CH_2C_6H_4$-pF	52
5b	$CH_2C_6H_3$-o,p$(OCH_3)_2$	67
5c	$(CH_2)_2C_6H_3$-m,p$(OCH_3)_2$	63
5d	C_6H_{13}	57
5e	C_6H_4-mCl	85
5f	$CH_2COOC_2H_5$	73
5g	$CH_2CH_2CH_2Cl$	69
5h	$OCH_2C_6H_5$	69

[a] Yields for the conversion of **3** into **4a-h**.

amine as a model, we synthesized the corresponding amide **8** in 42% yield. Cyclization of **8** was of particular interest since it may give either a five-membered ring (1-benzyloxy-3-arylsuccinimide **9**) or a seven-membered ring (a 2-benzazepine-1,3-dione **11**) depending on the reactivity of the two methyl ester functions (Fig. 1). With a 5 min reaction time, a mixture of **10** (80%) and **11** (20%) was obtained. Prolonging the reaction time (15 min) gave only quantitatively the 1,3-dioxo-2-benzazepine-5-carboxylic acid **10**.

To determine the structure of **10**, it was quantitatively converted into **11** using classical esterification

Scheme 3



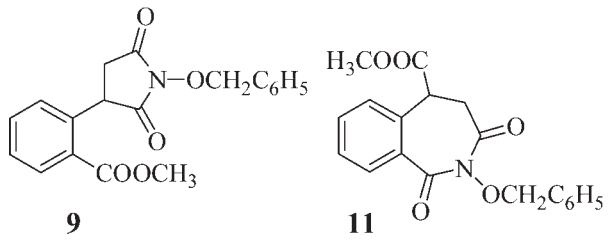


Figure 1. Possible products from the cyclization of **8**.

conditions. The benzazepine structure of **11** was established on the basis of ^{1}H-^{13}C correlation experiments. Briefly, the CO signal of the ester function (170.6 ppm) can be easily identified *via* the methyl group (3.57 ppm). This CO signal correlated with H-5 (4.23 ppm) which also gave a correlation with carbon 3 (168.5 ppm). On the other side, carbon 1 (161.1 ppm) gave correlations with H-9 and H-8 (8.27 and 7.30 ppm, respectively). The isolation of **10** as a single cyclized product clearly shows that the benzoic ester function of **8** was more reactive than the aliphatic one.

In conclusion, eight 2-substituted-4-methoxycarbonylisoquinoline-1,3-diones (substituents: alkyl, alkylaryl, aryl, benzyloxy, carboxymethylene) have been synthesized in a four-step procedure in overall yields ranging between 29 and 53%. Other alkoxycarbonyl groups may be introduced at position 4 (data not shown). This novel synthetic scheme employs four steps. In terms of yield, the introduction of the carboxylic acid function and the subsequent coupling with an amine are the two limiting steps whereas the two remaining ones are quantitative. In terms of cumulative reaction time, this novel route is undoubtedly more advantageous than route a (Scheme 1) starting from homophtalic acid derivatives, which requires much longer reaction times (4–72 h for the amine condensation and 3–24 h for the subsequent substitution) [1,3,5].

We compared our synthetic scheme to route b. Malamas *et al*. [1] reported the synthesis of **5** (R = CH_2-C_6H_4-oF-pBr) in 78% overall yield. Other analogues were also briefly described without any experimental information about the final cyclization step using variously substituted benzylamines and alkylamines. We compared the two routes for the synthesis of **5a**, **5d**, **5e**, and **5h**. Compounds **5a** and **5d** were synthesized by both methods with similar overall yields around 40%. In contrast our method was better than route b for the synthesis of **5e** and **5h**, which were obtained with 54 and 44% overall yields, respectively while route b failed to give these compounds. Crude residues contained mixtures of byproducts without any trace of the desired cyclized compound. So the two methods are comparable when the R substituent at position 2 is an alkyl or a benzyl group. When this substituent is an aryl or a benzyloxy group, our method is largely superior to route b. But the main advantage of our route over routes a and b lies in the clean, efficient and rapid last cyclization step, which is quantitatively performed within only 5 min reaction time. The homologation showed the better reactivity of the benzoate ester versus the malonate one and led also efficiently to the formation of a 5-carboxy-2-benzazepine-1,3-dione derivative. This route could also be employed and modified to synthesize variously substituted 2-benzazepine-1,3-diones since the elaboration of such compounds have been scarcely investigated. To the best of our knowledge, only diphenimides [11] and a few examples of 2- and 4-substituted derivatives have been so far reported [12,13].

EXPERIMENTAL

Silica gel, 200–400 mesh (Merck) was used for column chromatography. Melting points were obtained on a Reichert Thermopan melting point apparatus, equipped with a microscope. NMR spectra were obtained on an AC 300 Bruker spectrometer in the appropriate solvent with TMS as internal reference. J values are given in Hz. Elemental analyses were performed by CNRS laboratories (Vernaison) and were within 0.4% of the theoretical values.

Methyl 2-(2-methoxy-2-oxoethyl)benzoate (2). Homophtalic acid **1** (5 g, 28.0 mmol) was dissolved in MeOH (100 mL) and thionyl chloride (5.5 mL, 62.0 mmol) was added dropwise. The solution was heated under reflux for 2 h and concentrated *in vacuo*. The residue was dissolved in AcOEt and washed several times with 10% $NaHCO_3$. After drying over Na_2SO_4, the solvent was evaporated *in vacuo* to yield **2** as a yellow oil (99%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.60 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.00 (s, 2H, CH_2), 7.36 (m, 3H, H_{Ar}), 7.92 (dd, ^{3}J = 8.2 Hz, ^{4}J = 2.0 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 36.7 (CH_2), 51.4 (OCH_3), 51.8 (OCH_3), 127.4 (CH), 129.5 (C), 130.3 (CH), 132.4 (CH), 132.6 (CH), 135.9 (C), 166.9 (CO), 172.4 (CO).

3-Methoxy-2-[2-(methoxycarbonyl)phenyl]-3-oxopropanoic acid (3). A solution of freshly distilled diisopropylamine (0.75 mL, 5.35 mmol) in 10.0 mL of dry THF under an argon atmosphere was cooled to –78°C and 3.34 mL of 1.6*M* *n*-butyllithium (5.35 mmol) was added. After 30 min reaction at –78°C, a solution of **2** (0.79 g, 3.8 mmol) in 10.0 mL of THF was added dropwise. After stirring the solution for 30 min, the temperature had risen to –5°C and the argon inlet was removed. CO_2 formed from addition of sulfuric acid on anhydrous barium carbonate was bubbled through the reaction mixture for 20 min. The mixture was acidified with 2.0*M* HCl and then extracted with $CHCl_3$. The combined organic extracts were extracted with 10% Na_2CO_3. The basic extracts were made acidic by the careful addition of 2.0*M* HCl and the product was extracted into $CHCl_3$ (3 × 100 mL). The combined $CHCl_3$ extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure to give an oily residue, which crystallized on cooling. Orange solid (0.49 g; 62%); mp 100°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3H, OCH_3),

3.87 (s, 3H, OCH_3), 5.16 (s, 1H, CH), 7.38 (dd, ^3J = 7.7 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}), 7.44 (td, ^3J = 7.7 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}), 7.57 (td, ^3J = 7.7 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}), 8.07 (dd, ^3J = 7.7 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}), 11.22 (br s, 1H, COOH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.5 (OCH_3), 53.3 (OCH_3), 55.5 (CH), 128.5 (CH), 128.6 (C), 131.3 (CH), 132.3 (CH), 132.9 (CH), 134.4 (C), 167.7 (CO), 170.6 (CO), 170.8 (CO).

Methyl 2-{1-[(4-fluorobenzyl)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate (4a). BOP (1.69 g, 4.0 mmol) was added to an ice-cooled solution of **3** (1.00 g, 4.0 mmol), 4-fluorobenzylamine (0.50 g, 4.0 mmol) and 4-methylmorpholine (2.2 mL, 20.0 mmol) in a minimum of CH_2Cl_2. After 30 min stirring at 0°C and 3 h at room temperature, the mixture was washed with 1.0*M* HCl, 1.0*M* $NaHCO_3$ solutions and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. After column chromatography of the residue (eluent: petroleum ether/AcOEt, 70/30 then 50/50), the product was obtained as beige crystals (52%); mp 127°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.59 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.25 (dd, ^2J = 14.9 Hz, ^3J = 6.0 Hz, 1H, CH_2), 4.32 (dd, ^2J = 14.9 Hz, ^3J = 6.0 Hz, 1H, CH_2), 5.20 (s, 1H, CH), 6.85 (t, ^3J = 8.4 Hz, 2H, H_{Ar}), 7.08 (dd, ^3J = 8.8 Hz, ^4J = 5.4 Hz, 2H, H_{Ar}), 7.29 (td, ^3J = 7.5 Hz, ^4J = 2.0 Hz, 1H, H_{Ar}), 7.40–7.50 (m, 2H, H_{Ar}), 7.64 (t, ^3J = 5.3 Hz, 1H, NH), 7.87 (dd, ^3J = 7.6 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.7 (CH_2), 52.2 (OCH_3), 52.5 (OCH_3), 55.1 (CH), 115.1 (d, ^2J = 21.4 Hz, 2CH), 127.8 (CH), 128.8 (C), 129.0 (d, ^3J = 8.3 Hz, 2CH), 130.6 (CH), 131.6 (CH), 132.5 (CH), 133.9 (d, ^4J = 3.3 Hz, C), 135.5 (C), 161.8 (d, ^1J = 243.3 Hz, C), 167.3 (CO), 168.0 (CO), 170.1 (CO); *Anal*. Calc for $C_{19}H_{18}FNO_5$: C, 63.50; H, 5.05; O, 22.26. Found: C, 63.61; H, 5.09; O, 22.11.

Methyl 2-{1-[(2,4-dimethoxybenzyl)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate (4b). After column chromatography (eluent: petroleum ether/AcOEt, 50/50), the product was obtained as a yellow oil (67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.62 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.30 (d, ^3J = 5.7 Hz, 2H, CH_2), 5.30 (s, 1H, CH), 6.31 (dd, ^3J = 8.1 Hz, ^4J = 2.2 Hz, 1H, H_{Ar}), 6.34 (d, ^4J = 2.2 Hz, 1H, H_{Ar}), 7.05 (d, ^3J = 8.1 Hz, 1H, H_{Ar}), 7.30 (td, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.41–7.54 (m, 3H, NH, 2 H_{Ar}), 7.89 (dd, ^3J = 7.9 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.9 (CH_2), 52.0 (OCH_3), 52.2 (OCH_3), 54.9 (OCH_3), 55.0 (OCH_3), 55.1 (CH), 98.1 (CH), 103.5 (CH), 118.4 (C), 127.5 (CH), 129.0 (C), 129.8 (CH), 130.4 (CH), 131.2 (CH), 132.2 (CH), 135.3 (C), 158.2 (*C*—OCH_3), 160.1 (*C*—OCH_3), 166.8 (CO), 167.6 (CO), 169.9 (CO); *Anal*. Calc for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.78; O, 27.90. Found: C, 62.72; H, 5.68; O, 28.08.

Methyl 2-(1-{[2-(2,4-dimethoxyphenyl)ethyl]amino}-3-methoxy-1,3-dioxopropan-2-yl)benzoate (4c). Yellow oil (63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.70 (t, ^3J = 7.0 Hz, 2H, CH_2), 3.42 (dd, ^3J = 7.0 Hz, ^3J = 5.2 Hz, 2H, CH_2), 3.66 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 5.28 (s, 1H, CH), 6.57 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 6.66 (d, ^4J = 1.5 Hz, 1H, H_{Ar}), 6.69 (d, ^3J = 8.0 Hz, 1H, H_{Ar}), 7.24 (t, ^3J = 5.3 Hz, 1H, NH), 7.35 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.46–7.56 (m, 2H, 2 H_{Ar}), 7.91 (dd, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.9 (CH_2), 40.9 (CH_2), 52.1 (OCH_3), 52.3 (OCH_3), 54.7 (CH), 55.5 (OCH_3), 55.6 (OCH_3), 110.9 (CH), 111.6 (CH), 120.4 (CH), 127.6 (CH), 128.7 (C), 130.4 (CH), 131.1 (C), 131.2 (CH), 132.3 (CH), 135.3 (C), 147.2 (*C*—OCH_3), 148.5 (*C*—OCH_3), 167.3 (CO), 167.8 (CO), 169.5 (CO); *Anal*. Calc for $C_{22}H_{25}NO_7$: C, 63.60; H, 6.07; O, 26.96. Found: C, 63.51; H, 5.98; O, 27.12.

Methyl 2-[1-(hexylamino)-3-methoxy-1,3-dioxopropan-2-yl] benzoate (4d). After column chromatography (eluent: petroleum ether/AcOEt, 50/50), the product was obtained as a transparent oil (57%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, ^3J = 6.5 Hz, 3H, CH_3), 1.20–1.26 (m, 6 H, CH_2), 1.47 (m, 2H, CH_2), 3.22 (q, ^3J = 6.5 Hz, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.30 (s, 1H, CH), 7.19 (t, ^3J = 6.5 Hz, 1H, NH), 7.38 (td, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.52 (td, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.62 (dd, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.93 (dd, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.5 (CH_2), 26.4 (CH_2), 29.2 (CH_2), 31.3 (CH_2), 39.7 (CH_2), 52.4 (OCH_3), 52.5 (OCH_3), 54.9 (CH), 127.7 (CH), 128.5 (C), 130.6 (CH), 131.6 (CH), 132.5 (CH), 135.6 (C), 167.3 (CO), 168.2 (CO), 170.2 (CO); *Anal*. Calc for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; O, 23.85. Found: C, 64.72; H, 7.36; O, 23.62.

Methyl 2-{1-[(3-chlorophenyl)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate (4e). After column chromatography (eluent: petroleum ether/AcOEt, 50/50), the product was obtained as a transparent oil (85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.32 (s, 1H, CH), 7.05 (dd, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.29 (td, ^3J = 7.5 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}), 7.38 (dd, ^3J = 7.6 Hz, ^4J = 2.0 Hz, 1H, H_{Ar}), 7.42 (td, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.57 (td, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.64 (dd, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.69 (d, ^4J = 1.3 Hz, 1H, H_{Ar}), 7.98 (dd, ^3J = 7.6 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}), 9.76 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.7 (OCH_3), 52.9 (OCH_3), 56.1 (CH), 117.7 (CH), 119.8 (CH), 124.2 (CH), 128.2 (CH), 128.9 (C), 129.8 (CH), 130.8 (CH), 132.1 (CH), 132.8 (CH), 134.5 (C), 134.9 (C), 139.1 (C), 165.7 (CO), 168.7 (CO), 170.0 (CO); *Anal*. Calc for $C_{18}H_{16}ClNO_5$: C, 59.76; H, 4.46; O, 22.11. Found: C, 60.02; H, 4.70; O, 21.94.

Methyl 2-{1-[(2-ethoxy-2-oxoethyl)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate (4f). After column chromatography (eluent: petroleum ether/AcOEt, 50/50), the product was obtained as a white crystals (73%); mp 75°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (t, ^3J = 7.0 Hz, 3H, CH_3), 3.60 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.90 (t, ^3J = 5.3 Hz, 2H, CH_2), 4.06 (q, ^3J = 7.0 Hz, 2H, CH_2), 5.33 (s, 1H, CH), 7.28 (td, ^3J = 7.5 Hz, ^4J = 1.4 Hz, 1H, H_{Ar}), 7.44–7.50 (m, 2H, H_{Ar}), 7.69 (br t, ^3J = 5.3 Hz, 1H, NH), 7.87 (dd, ^3J = 7.5 Hz, ^4J = 1.4 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (CH_3), 41.6 (CH_2), 52.4 (OCH_3), 52.6 (OCH_3), 54.9 (CH), 61.3 (CH_2), 127.9 (CH), 129.1 (C), 130.7 (CH), 131.5 (CH), 132.5 (CH), 135.1 (C), 167.7 (CO), 168.0 (CO), 169.4 (CO), 169.9 (CO); *Anal*. Calc for $C_{16}H_{19}NO_7$: C, 56.97; H, 5.68; O, 33.20. Found: C, 56.73; H, 5.41; O, 33.39.

Methyl 2-{1-[(3-chloropropyl)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate (4g). Pale yellow crystals (69%); mp 84–85°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.94 (quin, ^3J = 6.5 Hz, 2H, CH_2), 3.37 (quin, ^3J = 6.7 Hz, 2H, CH_2), 3.50 (sext, ^3J = 5.4 Hz, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.86 (s, 3H,

OCH_3), 5.21 (s, 1H, CH), 7.37 (m, 1H, H_{Ar}), 7.48 (t, ^3J = 6.6 Hz, 1H, NH), 7.45 (m, 2H, H_{Ar}), 7.97 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.8 (CH_2), 36.9 (CH_2), 42.2 (CH_2), 52.3 (OCH_3), 52.5 (OCH_3), 55.2 (CH), 127.8 (CH), 128.8 (C), 130.6 (CH), 131.6 (CH), 132.5 (CH), 135.4 (C), 167.6 (CO), 168.0 (CO), 170.3 (CO); *Anal*. Calc for $C_{15}H_{18}ClNO_5$: C, 54.97; H, 5.54; O, 24.41. Found: C, 54.78; H, 5.39; O, 24.66.

Methyl 2-{1-[(benzyloxy)amino]-3-methoxy-1,3-dioxopropan-2-yl}benzoate (4h). After column chromatography (eluent: petroleum ether /AcOEt, 70/30), the product was obtained as a pale yellow oil (69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.63 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 4.79 (s, 2H, CH_2), 5.20 (s, 1H, CH), 7.18–7.28 (m, 5H, H_{Ar}), 7.33 (td, ^3J = 7.5 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}), 7.48 (td, ^3J = 7.5 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}), 7.57 (dd, ^3J = 7.5 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}), 7.87 (dd, ^3J = 7.5 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}), 9.64 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.5 (OCH_3), 52.7 (OCH_3), 52.8 (CH), 78.0 (OCH_2), 116.7 (C), 128.1 (CH), 128.5 (2CH), 128.6 (CH), 128.8 (C), 129.3 (2CH), 130.8 (CH), 131.9 (CH), 132.8 (CH), 134.5 (C), 165.4 (CO), 168.3 (CO), 169.3 (CO); *Anal*. Calc for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; O, 26.86. Found: C, 63.99; H, 5.62; O, 26.77.

Methyl 2-(4-fluorobenzyl)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5a). Compound **4a** (0.359 g, 1.0 mmol) was dissolved in a solution of methanol (10.0 mL) and 2.0*M* KOH (10.0 mL). After 5 min stirring, the solution was acidified with 2.0*M* HCl and extracted three times with ether (20.0 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to afford **5a** as off-white crystals (0.324 g, 99%); mp 167°C; 100% enol form. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98 (s, 3H, OCH_3), 5.30 (s, 2H, CH_2), 6.90 (t, ^3J = 8.4 Hz, 2H, H_{Ar}), 7.24 (td, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}), 7.41 (dd, ^3J = 8.8 Hz, ^4J = 5.4 Hz, 2H, H_{Ar}), 7.08 (dd, ^3J = 8.8 Hz, ^4J = 5.4 Hz, 2H, H_{Ar}), 7.54 (td, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}), 8.29 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}), 8.32 (dd, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.8 (CH_2), 52.7 (OCH_3), 84.8 (C), 115.1 (d, ^2J = 21.4 Hz, 2CH), 123.9 (CH), 124.3 (CH), 127.0 (C), 128.5 (CH), 130.6 (d, ^3J = 8.3 Hz, 2CH), 130.6 (CH), 132.2 (d, ^4J = 3.3 Hz, C), 135.5 (C), 162.0 (CO), 132.1 (d, ^1J = 241.3 Hz, C), 166.9 (CO), 173.8 (CO); *Anal*. Calc for $C_{18}H_{14}FNO_4$: C, 66.05; H, 4.31; O, 19.55. Found: C, 66.17; H, 4.15; O, 19.22.

Methyl 2-(2,4-dimethoxybenzyl)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5b). Off-white crystals (99%); mp 121°C; 85% enol form, 15% keto form. Enol form: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 5.40 (s, 2H, CH_2), 6.37 (dd, ^3J = 8.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 6.49 (d, ^4J = 1.5 Hz, 1H, H_{Ar}), 6.83 (d, ^3J = 8.3 Hz, 1H, H_{Ar}), 7.33 (td, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.64 (td, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.40–8.46 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 2H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.8 (CH_2), 52.8 ($COOCH_3$), 55.3 (OCH_3), 55.5 (OCH_3), 84.6 (C), 98.5 (CH), 104.2 (CH), 116.8 (C), 121.0 (C), 124.1 (CH), 124.3 (CH), 127.3 (CH), 128.7 (CH), 133.5 (CH), 133.8 (C), 157.9 (*C*—OCH_3), 160.1 (*C*—OCH_3), 162.0 (CO), 164.4 (CO), 173.9 (CO); Keto form: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.97 (s, 1H, CH), 5.15 (d, ^2J = 15.1 Hz, 1H, CH_2), 5.26 (d, ^2J = 15.1 Hz, 1H, CH_2), 6.38–6.50 (m, 2H, H_{Ar}), 7.07 (d, ^3J = 8.3 Hz, 1H, H_{Ar}), 7.33 (td, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.45 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.52 (td, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.26 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.9 (CH_2), 53.5 (OCH_3), 53.7 (OCH_3), 55.3 (OCH_3), 55.5 (CH), 98.4 (CH), 103.9 (CH), 116.8 (C), 125.2 (C), 126.9 (CH), 128.3 (CH), 128.9 (CH), 129.6 (CH), 132.1 (C), 134.0 (CH), 158.1 (*C*—OCH_3), 160.1 (*C*—OCH_3), 164.0 (CO), 166.7 (CO), 167.5 (CO); *Anal*. Calc for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; O, 25.99. Found: C, 65.34; H, 5.09; O, 25.72.

Methyl 2-[2-(3,4-dimethoxyphenyl)ethyl]-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5c). Beige crystals (99%); mp 101°C; 90% enol form, 10% keto form. Enol form: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.93 (t, ^3J = 8.0 Hz, 2H, CH_2), 3.84 (s, 6H, 2 × OCH_3), 4.03 (s, 3H, OCH_3), 4.35 (t, ^3J = 8.0 Hz, 2H, CH_2), 6.75–6.88 (m, 3H, H_{Ar}), 7.28 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.58 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.33 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}), 8.35 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.6 (CH_2), 43.0 (CH_2), 52.6 (OCH_3), 55.6 (OCH_3), 55.7 (OCH_3), 84.3 (C), 111.0 (CH), 111.8 (CH), 120.6 (C), 120.7 (CH), 123.8 (CH), 124.1 (CH), 128.2 (CH), 130.6 (C), 133.2 (CH), 133.4 (C), 147.5 (C—OH), 148.7 (C—OH), 161.5 (CO), 163.8 (CO), 173.7 (CO); Keto form: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.87 (t, ^3J = 7.7 Hz, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.84 (s, 6H, 2 × OCH_3), 4.20 (t, ^3J = 7.7 Hz, 2H, CH_2), 4.88 (s, 1H, CH), 6.75–6.88 (m, 3H, H_{Ar}), 7.40 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}), 7.49 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.58 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.21 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.4 (CH_2), 41.8 (CH_2), 53.4 (OCH_3), 53.5 (OCH_3), 55.8 (OCH_3), 55.9 (CH), 111.2 (CH), 111.8 (CH), 120.6 (CH), 125.0 (C), 126.9 (CH), 128.9 (CH), 129.3 (CH), 130.9 (C), 133.2 (C), 134.0 (CH), 147.6 (C—OH), 148.8 (C—OH), 163.8 (CO), 166.8 (CO), 167.4 (CO); *Anal*. Calc for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; O, 25.04. Found: C, 65.65; H, 5.23; O, 24.91.

Methyl 2-hexyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5d). Purple crystals (99%); mp 88°C; 90% enol form, 10% keto form. Enol form: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 7.1 Hz, 3H, CH_3), 1.30–1.43 (m, 6H, 3 × CH_2), 1.71 (m, 2H, CH_2), 4.04 (s, 3H, OCH_3), 4.16 (t, ^3J = 7.6 Hz, 2H, CH_2), 7.29 (td, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.59 (td, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.33–8.38 (2dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 2H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8 (CH_3), 23.2 (CH_2), 26.6 (CH_2), 28.0 (CH_2), 31.5 (CH_2), 41.8 (CH_2), 52.7 (OCH_3), 84.4 (C), 120.9 (C), 124.0 (CH), 124.2 (CH), 128.4 (CH), 133.3 (C), 133.7 (C), 161.9 (CO), 164.2 (CO), 174.0 (CO); Keto form: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, ^3J = 7.1 Hz, 3H, CH_3), 1.30–1.43 (m, 6H, 3 × CH_2), 1.71 (m, 2H, CH_2), 3.21 (t, ^3J = 7.0 Hz, 2H, CH_2), 3.73 (s, 3H, OCH_3), 5.91 (s, 1H, CH), 7.29 (td, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.42 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.50 (td, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.23 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8 (CH_3), 23.2 (CH_2), 26.6 (CH_2), 27.7 (CH_2), 29.6 (CH_2), 40.7 (CH_2), 52.7 (OCH_3), 53.5 (CH), 125.1 (C), 126.9 (CH), 128.9 (CH), 129.4 (CH), 132.0 (C), 133.9 (C), 162.1 (CO), 166.9 (CO), 167.5 (CO); *Anal*. Calc for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; O, 21.10. Found: C, 67.05; H, 7.15; O, 21.27.

Methyl 2-(3-chlorophenyl)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5e). White crystals (99%); mp 128°C; 100% enol. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.09 (s, 3H, OCH_3), 7.23 (td, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.35–7.38 (m, 2H, H_{Ar}), 7.48–7.51 (m, 2H, H_{Ar}), 7.68 (td, ^3J = 7.7 Hz, ^4J = 1.4 Hz, 1H, H_{Ar}), 8.38 (dd, ^3J = 8.0 Hz, ^4J = 1.3 Hz, 1H, H_{Ar}), 8.48 (dd, ^3J = 8.3 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.1 (OCH_3), 84.8 (C), 121.2 (C), 124.4 (CH), 124.8 (CH), 126.9 (CH), 128.8 (CH), 128.9 (CH), 129.4 (CH), 130.4 (CH), 133.9 (C), 134.1 (CH), 134.9 (CH), 135.9 (C), 161.9 (CO), 163.7 (CO), 173.9 (CO); *Anal*. Calc for $C_{17}H_{12}ClNO_4$: C, 61.92; H, 3.67; O, 19.41. Found: C, 61.63; H, 3.55; O, 19.36.

[4-(methoxycarbonyl)-1,3-dioxo-3,4-dihydroisoquinolin-2(1*H*)-yl]acetic acid (5f). Off-white crystals (99%); mp 175°C; 50% enol form, 50% keto form. We give the NMR data of the keto/enol mixture since the contributions of the two forms exhibited strong overlaps. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.70 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.54 (d, ^2J = 15.0 Hz, 1H, CH_2), 4.59 (d, ^2J = 15.0 Hz, 1H, CH_2), 4.80 (s, 2H, CH_2), 5.50 (s, 1H, CH), 7.40 (td, ^3J = 7.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.46 (dd, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.61 (td, ^3J = 7.5 Hz, ^4J = 1.3 Hz, 1H, H_{Ar}), 7.72–7.80 (2td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 2H, H_{Ar}), 8.13 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.20 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.41 (dd, ^3J = 7.8 Hz, ^4J = 1.4 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 41.7 (CH_2), 42.7 (CH_2), 53.2 (CH), 53.8 (OCH_3), 53.9 (OCH_3), 84.4 (C), 121.2 (C), 124.4 (C), 124.5 (CH), 125.1 (CH), 127.8 (CH), 128.4 (CH), 129.0 (CH), 129.4 (CH), 133.3 (C), 133.8 (C), 134.5 (CH), 135.1 (CH), 161.1 (CO), 163.2 (CO), 163.8 (CO), 167.0 (CO), 167.8 (CO), 169.2 (CO), 169.4 (CO), 173.5 (CO); *Anal*. Calc for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; O, 34.63. Found: C, 56.05; H, 4.29; O, 34.74.

Methyl 2-(3-chloropropyl)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5g). Pale yellow crystals (99%); mp 98°C; 95% enol, 5% keto form. We give the NMR data of the keto/enol mixture since the contributions of the two forms exhibited strong overlaps. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.23 (quin, ^3J = 7.0 Hz, 2H, CH_2), 3.64 (t, ^3J = 6.6 Hz, 2H, CH_2), 4.07 (s, 3H, OCH_3), 4.35 (t, ^3J = 7.2 Hz, 2H, CH_2), 4.92 (s, 1H, CH), 7.32 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.45 (dd, ^3J = 7.7 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}), 7.53 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.62 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.25 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}), 8.34 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 8.39 (dd, ^3J = 7.8 Hz, ^4J = 1.6 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$):δ = 31.1 (CH_2), 39.6 (CH_2), 42.4 (CH_2), 52.9 (OCH_3), 84.6 (C), 120.7 (C), 124.1 (CH), 124.4 (CH), 128.5 (CH), 133.6 (CH), 133.6 (C), 161.9 (CO), 164.0 (CO), 174.0 (CO); *Anal*. Calc for $C_{14}H_{14}ClNO_4$: C, 56.86; H, 4.77; O, 21.64. Found: C, 56.65; H, 4.63; O, 21.80.

Methyl 2-(benzyloxy)-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (5h). Purple crystals (99%); mp 126°C; 82% enol, 18% keto form. We give the ^{1}H NMR data of the keto/enol mixture since the contributions of the two forms exhibited strong overlaps. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (s, 3H, OCH_3), 4.11 (s, 3H, OCH_3), 5.03 (s, 1H, CH), 5.29 (s, 2H, CH_2), 6.37 (dd, ^3J = 8.5 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.25 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.29–7.65 (m, 7H, H_{Ar}), 8.45 (m, 2H, H_{Ar}); Enol form: ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.1 (CH_3), 79.0 (CH_2), 84.3 (C), 121.2 (C), 124.3 (CH), 124.6 (CH), 128.3 (CH), 128.6 (2CH), 129.4 (CH), 130.1 (2CH), 132.9 (C), 133.5 (C), 133.8 (CH), 158.8 (CO), 163.0 (CO), 173.5 (CO); Keto form: ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.8 (CH_3), 54.8 (CH), 78.5 (CH_2), 119.3 (C), 123.5 (C), 127.3 (CH), 128.5 (2CH), 129.2 (CH), 129.3 (CH), 129.5 (CH), 130.0 (2CH), 131.4 (C), 133.5 (C), 134.4 (CH), 160.7 (CO), 162.9 (CO), 171.6 (CO); *Anal*. Calc for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65; O, 24.59. Found: C, 66.52; H, 4.94; O, 24.51.

Methyl 2-(1-methoxy-1-oxopent-4-en-2-yl)benzoate (6). A solution of freshly distilled diisopropylamine (0.75 mL, 5.35 mmol) in 10.0 mL of dry THF under an argon atmosphere was cooled to –78°C and 3.34 mL of 1.6*M* *n*-butyllithium (5.35 mmol) in THF was added. After 20 min reaction at –78°C, a solution of **2** (0.79 g, 3.8 mmol) in 10.0 mL of THF was added dropwise. After stirring the solution for 30 min at –78°C, allyl bromide (0.66 mL, 7.6 mmol) was added dropwise. Stirring was pursued 1 h at –78°C and then 1 h at room temperature. The reaction was quenched with NH_4Cl and the solution was extracted several times with ether. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: petroleum ether/AcOEt, 80/20) to give **6** as an orange oil (80%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (m, 1H, CH_2), 2.71 (m, 1H, CH_2), 3.45 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 4.60 (t, ^3J = 7.6 Hz, 1H, CH), 4.81 (dd, ^3J = 10.8 Hz, ^2J = 2.0 Hz, 1H, CH), 4.88 (dd, ^3J = 17.5 Hz, ^2J = 2.0 Hz, 1H, CH), 5.54–5.74 (m, 1H, CH), 7.12 (td, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.28 (m, 2H, H_{Ar}), 7.75 (dd, ^3J = 7.7 Hz, ^4J = 1.2 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.2 (CH_2), 46.5 (CH), 51.4 (OCH_3), 51.6 (OCH_3), 116.4 (=CH_2), 126.6 (CH), 128.4 (CH), 129.3 (C), 130.3 (CH), 131.8 (CH), 135.1 (C), 139.6 (C), 167.2 (CO), 173.3 (CO); *Anal*. Calc for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50; O, 25.78. Found: C, 67.95; H, 6.28; O, 25.59.

4-Methoxy-3-[2-(methoxycarbonyl)phenyl]-4-oxobutanoic acid (7). To **6** (1.6 g, 6.0 mmol) in *t*-BuOH (10.0 mL) was added a solution of K_2CO_3 (2.49 g, 18.0 mmol) in H_2O (20 mL). To the resulting mixture were added KIO_4 (4.14 g, 18.0 mmol) and $KMnO_4$ (0.66 g, 4.2 mmol). After stirring for 1 h at room temperature, the mixture was extracted with AcOEt and this organic layer was discarded. The aqueous layer was acidified with concentrated HCl solution and again exhaustively extracted with AcOEt. The combined organic layers were dried over Na_2SO_4 and evaporation of the solvent *in vacuo* gave an oil which crystallized on standing. The obtained beige crystals were carefully rinsed with ether (63%); mp 144°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.80 (dd, ^2J = 17.4 Hz, ^3J = 5.0 Hz, 1H, CH_2), 3.25 (dd, ^2J = 17.3 Hz, ^3J = 9.2 Hz, 1H, CH_2), 3.69 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.99 (dd, ^3J = 9.2 Hz, ^3J = 5.0 Hz, 1H, CH), 7.28–7.39 (m, 2H, H_{Ar}), 7.50 (td, ^3J = 7.5 Hz, ^4J = 1.3 Hz, 1H, H_{Ar}), 7.97 (dd, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 9.58 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.6 (CH_2), 44.1 (CH), 52.3 (OCH_3), 52.4 (OCH_3), 127.6 (CH), 129.1 (CH), 129.2 (C), 131.2 (CH), 132.7 (CH), 139.0 (C), 167.6 (CO), 173.4 (CO), 177.7 (CO); *Anal*. Calc for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30; O, 36.06. Found: C, 58.87; H, 5.18; O, 36.25.

Methyl 2-{4-[(benzyloxy)amino]-1-methoxy-1,4-dioxobutan-2-yl}benzoate (8). Same method as for the preparation of **4a**. Yellow oil (42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48

(dd, ^2J = 15.1 Hz, ^3J = 5.9 Hz, 1H, CH_2), 2.94 (dd, ^2J = 15.1 Hz, ^3J = 7.8 Hz, 1H, CH_2), 3.53 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.69 (d, ^2J = 11.1 Hz, 1H, OCH_2), 4.76 (d, ^2J = 11.1 Hz, 1H, OCH_2), 4.99 (t, ^3J = 6.9 Hz, 1H, CH), 7.20–7.30 (m, 7H, H_{Ar}), 7.39 (td, ^3J = 7.5 Hz, ^4J = 1.3 Hz, 1H, H_{Ar}), 7.86 (dd, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 9.47 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.9 (CH_2), 44.5 (CH), 51.7 (OCH_3), 51.8 (OCH_3), 77.5 (OCH_2), 127.0 (CH), 127.9 (2CH), 128.0 (CH), 128.8 (2CH), 128.8 (C), 129.7 (CH), 130.7 (CH), 132.1 (CH), 135.1 (C), 138.9 (C), 167.3 (CO), 168.3 (CO), 173.0 (CO); *Anal*. Calc for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; O, 25.85. Found: C, 64.77; H, 5.91; O, 25.64.

2-(Benzyloxy)-1,3-dioxo-2,3,4,5-tetrahydro-1*H*-2-benzazepine-5-carboxylic acid (10). Compound **8** was reacted for 15 min with a 2.5*M* KOH solution in aqueous methanol and, after the usual work-up (see preparation of **5a**), an oil was obtained, which crystallized on standing. The white crystals were washed with ether (80 %); mp 94–95°C. ^{1}H NMR (300 MHz, CD_3COCD_3): δ = 3.43 (dd, ^2J = 11.8 Hz, ^3J = 4.2 Hz, 1H, CH_2), 3.57 (dd, ^2J = 12.0 Hz, ^3J = 4.3 Hz, 1H, CH_2), 4.45 (t, ^3J = 4.3 Hz, 1H, CH), 5.11 (s, 2H, OCH_2), 7.37–7.48 (m, 3H, H_{Ar}), 7.54 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.60–7.69 (m, 3H, H_{Ar}), 7.73 (td, ^3J = 7.5 Hz, ^4J = 1.3 Hz, 1H, H_{Ar}), 8.19 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 11.0 (s, 1H, OH); ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 37.5 (CH_2), 43.3 (CH), 77.7 (OCH_2), 126.8 (C), 127.2 (CH), 128.2 (CH), 128.7 (CH), 128.9 (2CH), 129.3 (CH), 130.1 (2CH), 134.4 (CH), 135.7 (C), 138.7 (C), 164.2 (CO), 169.2 (CO), 172.0 (CO); *Anal*. Calc for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.65; O, 24.59. Found: C, 66.59; H, 4.74; O, 24.35.

Methyl 2-(benzyloxy)-1,3-dioxo-2,3,4,5-tetrahydro-1*H*-2-benzazepine-5-carboxylate (11). Compound **11** was reacted for 5 min with a 2.5*M* KOH solution in aqueous methanol to give a yellow oil (20%). Esterification of **10** with methanolic thionyl chloride (1 h reflux) also yielded quantitatively **11**. ^{1}H NMR (300 MHz, CD_3COCD_3): δ = 3.12 (dd, ^2J = 17.2 Hz, ^3J = 4.5 Hz, 1H, CH_2), 3.51 (dd, ^2J = 17.2 Hz, ^3J = 4.5 Hz, 1H, CH_2), 3.57 (s, 3H, OCH_3), 4.23 (t, ^3J = 4.5 Hz, 1H, CH), 5.14 (d, ^2J = 8.9 Hz, 1H, OCH_2), 5.18 (d, ^2J = 8.9 Hz, 1H, OCH_2), 7.30 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}), 7.35–7.43 (m, 3H, H_{Ar}), 7.49 (td, ^3J = 7.6 Hz, ^4J = 1.3 Hz, 1H, H_{Ar}), 7.60–7.65 (m, 3H, H_{Ar}), 8.27 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, CD_3COCD_3): δ = 37.8 (CH_2), 42.9 (CH), 52.2 (OCH_3), 78.1 (OCH_2), 125.7 (C), 126.1 (CH), 128.2 (CH), 128.5 (2CH), 129.0 (CH), 129.2 (CH), 129.9 (2CH), 134.1 (CH), 134.1 (C), 136.6 (C), 161.1 (CO), 168.5 (CO), 170.6 (CO); *Anal*. Calc for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; O, 23.57. Found: C, 67.02; H, 5.09; O, 23.45.

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