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**SYNTHESIS OF NITROGEN HETEROCYCLES BY
 INTRAMOLECULAR CYCLIZATION OF ALKENYL
 N-ACYLAMINOPHTHALIMIDES USING PHENYLIODINE(III)
 BIS(TRIFLUOROACETATE) (PIFA)**

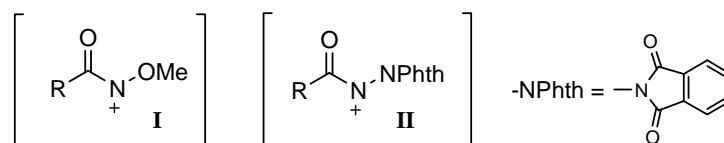
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Abstract – PIFA-mediated intramolecular cyclization of alkenyl *N*-acylaminophthalimides leads to the formation of a new C-N bond via an *N*-acyl-*N*-phthalimidonitrenium ion intermediate. The reaction pathway also results in the introduction of an oxygen function into the molecule giving added versatility to this single step procedure.

Nitrogen heterocyclic compounds occur in a large number of natural products and pharmaceutical drugs. Therefore, development of new routes to this class of compounds continues to be an important area of synthetic organic chemistry. In our own research to this end we have investigated the synthetic utility of positively charged nitrogen species (nitrenium ions) and have reported new syntheses of benzene fused *N*-heterocycles by intramolecular aromatic substitution with *N*-methoxy-*N*-acylnitrenium¹ and *N*-phthalimido-*N*-acylnitrenium² ions (**I** and **II**). In the former case we utilized PIFA to generate *N*-methoxy-*N*-acylnitrenium ions directly from the corresponding amides.³



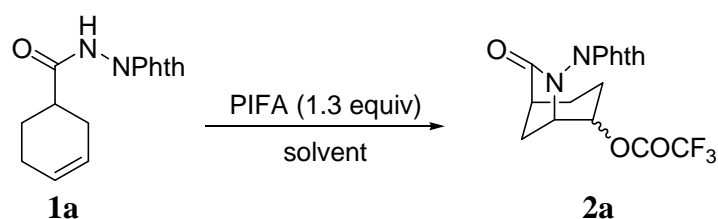
Very recently we reported the intermolecular reaction of styrenes with *N*-acetylaminophthalimide mediated by PIFA to produce 2-(*N*-acetylaminophthalimido)aminoethyl trifluoroacetates in high yield.⁴

We now wish to describe intramolecular ring closure reactions which take place by electrophilic attack of a nitrogen electrophile (nitrenium ion) on a neighboring double bond. This results in a convenient synthetic pathway for the preparation of a variety of nitrogen heterocycles.

Reports of ring closure reactions initiated by an internal nitrogen electrophile with formation of a new carbon-nitrogen bond are rare. Gassman, *et al.* reported the first example of such an intramolecular addition of a nitrenium ion to a carbon-carbon double bond.⁵ Recently Tellitu and Domínguez reported an intramolecular PIFA mediated alkene amidation through an *N*-aryl-*N*-acylnitrenium ion intermediate.⁶ For the success of the reaction the generated nitrenium ion should be stabilized such that there is a sufficient life-time to react with a C-C double bond. Therefore, the selection of the appropriate N-substituent is of key importance.

Initially, we examined the reaction of *N*-methoxy(cyclohex-3-ene)carboxamide with PIFA in chloroform. However, the resulting reaction mixture contained complex mixtures of unidentified products (TLC). In contrast, when we changed the N-substituent of the starting compound from an *N*-methoxy to an *N*-phthalimido group, the ring closure reaction went smoothly and the reaction mixture contained a single product (TLC), the structure of which was determined to be **2a**. Therefore, we examined in greater detail of the reaction of *N*-phthalimido(cyclohex-3-ene)carboxamide (**1a**) with PIFA in order to optimize the experimental conditions. The results are presented in Table 1.

Table 1. Reaction of *N*-phthalimido(cyclohex-3-ene)carboxamide (**1a**) with PIFA in various solvents

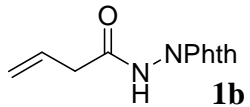
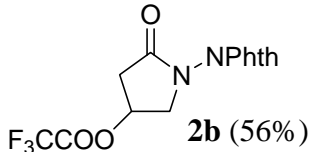
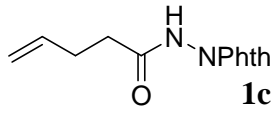
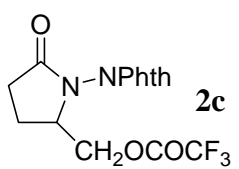
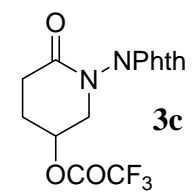
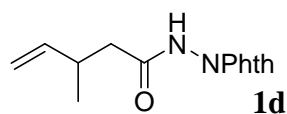
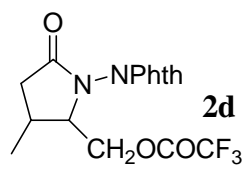
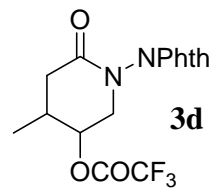
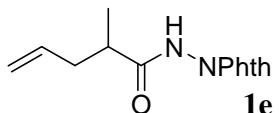
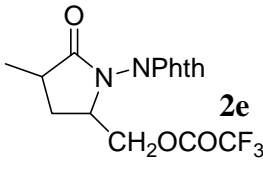
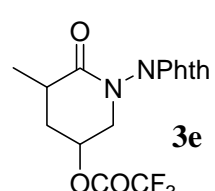
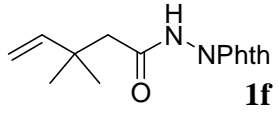
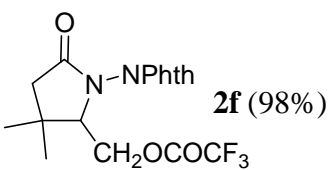
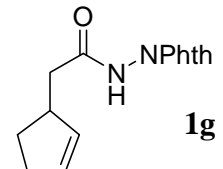
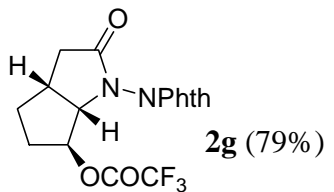
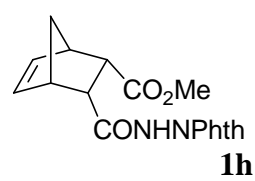
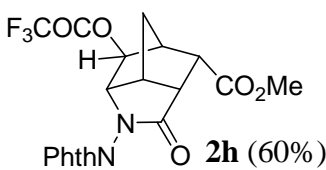
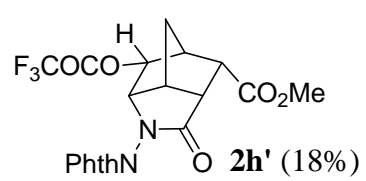


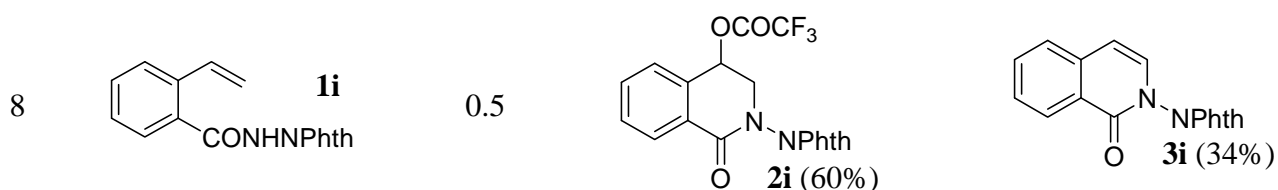
entry	solvent	temp (°C)	time (h)	yield (%)
1 ^a	CHCl ₃	r.t.	4	89
2	CHCl ₃	refl.	0.5	97
3	CH ₂ Cl ₂	refl.	0.5	97
4	ClCH ₂ CH ₂ Cl	refl.	0.5	88
5	MeCN	refl.	0.5	19
6	CF ₃ CO ₂ H	r.t.	10 ^b	trace
7	CF ₃ CH ₂ OH	r.t.	24	trace
8	(CF ₃) ₂ CHOH	r.t.	1	trace

^a 1.1 Equivalent of PIFA was used. ^b Minutes.

Since halogenated solvents consistently gave good results, the cyclization reactions of other starting compounds (**1b** – **i**) were carried out under the condition of entry 2 (Table 1). The results are presented in Table 2.

Table 2. Intramolecular cyclization of alkenyl *N*-acylaminophthalimides using PIFA

entry	starting material	time (h)	product yield (%)
1		1	 2b (56%)
2		0.5	 2c  3c 2c + 3c (92%) (2c : 3c = 3 : 1) ^a
3		0.5	 2d  3d 2d + 3d (93%) (2d : 3d = 9 : 1) ^a
4		0.5	 2e  3e 2e + 3e (90%) (2e : 3e = 9 : 1) ^a
5		0.5	 2f (98%)
6		0.5	 2g (79%)
7		0.5	 2h (60%)  2h' (18%)

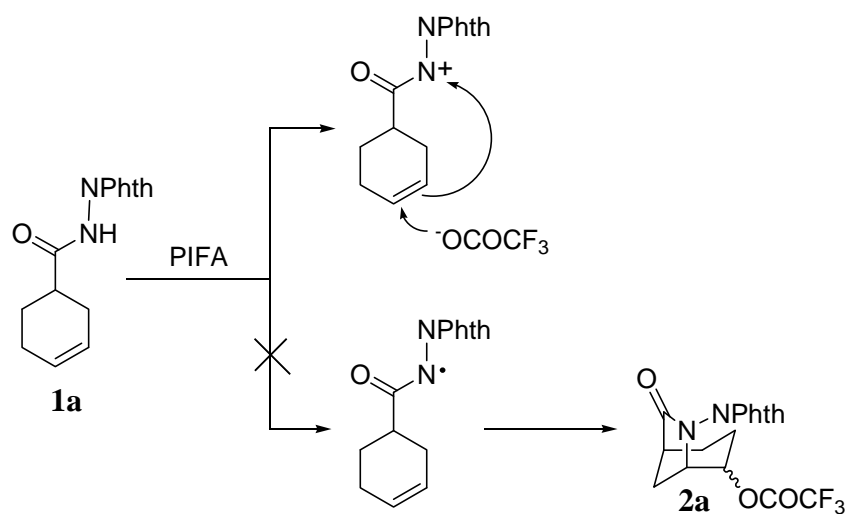


^a These product ratios were determined by ¹H NMR integration of the C-5 methine protons of **3c-e** which appear at 5.24-5.61 ppm apart from other proton signals.

In this reaction the *N*-acyl-*N*-phthalimidonitrenium ion (**II**) generated by the action of PIFA on the starting compound can be trapped by the olefin present in the molecule by a 5-*exo*-trig cyclization mode. The resulting carbocation can be subsequently captured by a free trifluoroacetate anion to afford the product. In general, a 5-*exo*-trig closure rather than a 6-*endo*-trig path will be more favorable and formation of a five-membered ring is preferred over a six-membered ring.⁷ Consistent with this, a five-membered ring forms preferentially in the above examples (Table 2, entries 1 - 7). On the other hand, in the case of 2-vinyl-*N*-phthalimidobenzamide (**1i**) isoquinolinone derivatives (**2i** and **3i**) were obtained in quantitative combined yield without formation of a five-membered ring (entry 8).

Formation of **2i** and **3i** can be explained as follows. The reaction proceeds in an intramolecular electrophilic attack of the nitrenium ion to the double bond, and the created carbocationic species can be captured by a free trifluoroacetate anion to afford **2i** or quenched by the elimination of an adjacent hydrogen to afford **3i**. Serna *et al.* reported^{6c} that in the case of 2-vinyl-*N*-(4-methoxyphenyl)benzamide the 5-*exo*-trig cyclization took place to afford the isoindolinone derivative through an aziridinium ion intermediate.⁸ Furthermore they reported in the reaction mixture the presence of trace amounts of the dimeric compound which would be derived from a radical mechanism.^{6c}

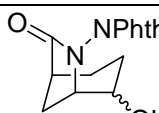
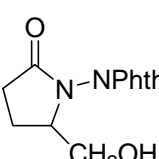
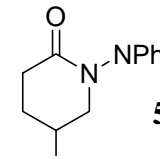
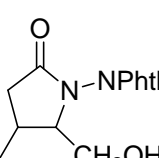
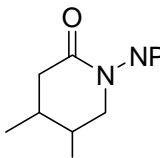
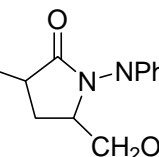
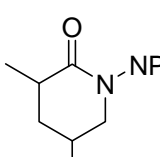
In our case, an addition of a radical scavenger *N,N*-diphenylpicrylhydrazil⁹ had no effect on the cyclization reaction. Therefore, a radical mechanism is not supported in our case, although the presence of an aziridinium ion intermediate is not completely excluded. These differences suggest the requirement for a proper electronic environment surrounding the positive nitrogen. Although the reason for this rather peculiar requirement remains unknown, we suspect that the phthalimido moiety of **II** assumes a strong stabilizing role for a nitrenium ion in the reaction. The described transformation exemplified by the reaction of **1a** can be rationalized as depicted in Scheme 1.

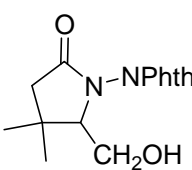
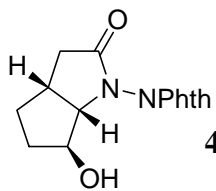
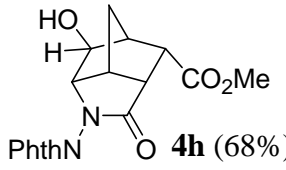
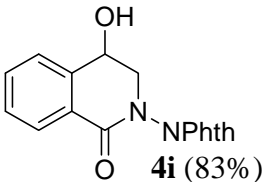


Scheme 1

The trifluoroacetyl groups of **2** and **3** were removed under mildly acidic conditions to afford **4** and **5**, respectively. The two protective groups were removed directly using hydrazine monohydrate in ethanol. The results are presented in Table 3 and Table 4.

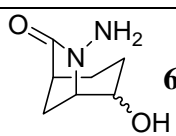
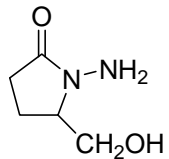
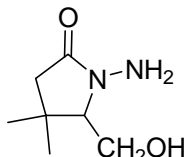
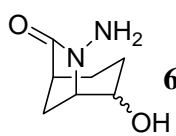
Table 3. Removal of trifluoroacetyl group under acidic conditions^a

entry	starting material	time (min)	product yield (%)	
1	2a	30	 4a (81%)	<i>endo</i> : <i>exo</i> = 2 : 1
2	2c + 3c	10	 4c	 5c 4c + 5c (76%) (4c : 5c = 3 : 1)
3	2d + 3d	10	 4d	 5d 4d + 5d (84%) (4d : 5d = 5 : 1)
4	2e + 3e	10	 4e	 5e 4e + 5e (85%) (4e : 5e = 6 : 1)

5	2f	60		4f (76%)
6	2g	30		4g (87%)
7	2h	30		4h (68%)
8	2i	15		4i (83%)

^a Reaction conditions: in AcOH-THF-H₂O (3:1:1) at 70 °C.

Table 4. Removal of phthaloyl group with hydrazine monohydrate

entry	starting material	H ₂ NNH ₂ ·H ₂ O (equiv)	time (min)	product yield (%)
1	2a	5.0	30	 6a (88%)
2	4c	2.5	30	 6c (73%)
3	4f	2.5	30	 6f (75%)
4	4a	2.5	30	 6a (71%)

In conclusion, intramolecular cyclization of an internal nitrogen electrophile was initiated by the action of PIFA on precursor alkenyl *N*-acylaminophthalimides. This provides a facile synthesis of lactams through 5-*exo*-trig and 6-*endo*-trig processes. The procedure is operationally extremely simple and offers an easy access to a wide range of substituted lactams.

EXPERIMENTAL

All melting points were determined on a micro hot-stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM-EX270 or JNM-A500 spectrometers with tetramethylsilane (MeSi_4) as an internal reference. IR spectra were measured at a JASCO IR 810 spectrophotometer. MS spectra were obtained with a JEOL JMX-DX 300 spectrometer with a direct inlet system at 70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this University.

Preparation of *N*-(1,3-dioxoisindolin-2-yl)cyclohex-3-enecarboxamide (**1a**): Typical Procedure for

Starting Materials. EDCI (1973 mg, 10.3 mmol) was added to a solution of cyclohex-3-ene-1-carboxylic acid (1000 mg, 7.92 mmol) and *N*-aminophthalimide (1284 mg, 7.92 mmol) in pyridine (50 mL). The reaction mixture was stirred for 24 h at rt. After the reaction was complete, the solvent was removed *in vacuo* and 10% HCl (80 mL) was added. The mixture was extracted with EtOAc (3 x 50 mL) and the combined organic solvent was washed with 10% aq Na_2CO_3 (2 x 50 mL), brine (2 x 50 mL), and dried over Na_2SO_4 , and concentrated. The residue was purified by column chromatography on silica gel using 50% EtOAc-hexane to give the product **1a** (1817 mg, 85%). **1a**: colorless crystals, mp 172-173 °C (EtOAc-hexane); IR (KBr) 3250, 1800, 1750, 1680, 1520, 1205, 880, 705 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.77-2.76 (m, 7H), 5.75 (s, 2H), 7.57 (br s, 1H), 7.72-7.98 (m, 4H); ^{13}C NMR (68 MHz, CDCl_3) δ 24.25, 25.53, 27.62, 39.03, 123.85, 124.76, 126.87, 129.89, 134.55, 165.08, 174.46; EIMS m/z 270 (M^+ , 12.5), 163 (100), 108 (26.0), 81 (64.8). Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.76; H, 5.09; N, 10.26.

The other starting materials **1b-g** were prepared following the same procedure described for **1a**.

***N*-(1,3-Dioxoisindolin-2-yl)but-3-enamide (1b).** Yield 60%, colorless crystals, mp 178-183 °C (EtOAc-hexane); IR (KBr) 3270, 3000, 1800 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 3.26 (d, $J = 6.9$ Hz, 2H), 5.29-5.50 (m, 2H), 5.95-6.14 (m, 1H), 7.60 (br s, 1H), 7.74-7.99 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ 38.98, 120.81, 124.26, 129.54, 130.00, 164.42, 169.28; EIMS m/z 230 (M^+ , 5.7), 162 (100), 104 (19.3), 68 (10.5). Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.61; H, 4.19; N, 12.19.

***N*-(1,3-Dioxoisindolin-2-yl)pent-4-enamide (1c).** Yield 78%, colorless crystals, mp 120-121 °C (EtOAc-hexane); IR (KBr) 3275, 2990, 1800, 1750, 1675, 1515, 1390, 1210, 885, 710 cm^{-1} ; ^1H NMR

(270 MHz, CDCl₃) δ 2.52 (s, 4H), 4.91-5.24 (m, 2H), 5.72-6.02 (m, 1H), 7.56 (br s, 1H), 7.70-8.02 (m, 4H); ¹³C NMR (68 MHz, CDCl₃) δ 28.95, 33.10, 116.04, 123.87, 129.82, 134.58, 136.09, 165.03, 171.06; EIMS m/z 244 (M⁺, 0.3), 214 (4.4), 162 (100), 104 (19.8), 83 (7.2). Anal. Calcd for C₁₃H₁₂N₂O₃: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.82; H, 4.89; N, 11.42.

***N*-(1,3-Dioxoisindolin-2-yl)-3-methylpent-4-enamide (1d)**. Yield 84%, colorless crystals, mp 136-137 °C (EtOAc-hexane); IR (KBr) 3260, 3000, 2970, 1800, 1750, 1670, 1515, 1210, 885, 710 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.13 (d, J = 7.1 Hz, 3H), 2.26-2.54 (m, 2H), 2.65-2.85 (m, 1H), 4.97-5.17 (m, 2H), 5.76-5.93 (m, 1H), 7.71-7.92 (m, 4H), 8.00 (br s, 1H); ¹³C NMR (68 MHz, CDCl₃) δ 19.24, 34.34, 40.69, 113.80, 123.75, 129.72, 134.45, 141.82, 164.90, 170.40; EIMS m/z 258 (M⁺, 0.7), 162 (100), 96 (9.0), 69 (21.7). Anal. Calcd for C₁₄H₁₄N₂O₃: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.89; H, 5.42; N, 10.85.

***N*-(1,3-Dioxoisindolin-2-yl)-2-methylpent-4-enamide (1e)**. Yield 70%, colorless crystals, mp 139-140 °C (EtOAc-hexane); IR (KBr) 3230, 3025, 1800, 1745, 1680, 1220, 885, 710 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.29 (d, J = 6.8 Hz, 3H), 2.21-2.38 (m, 1H), 2.44-2.67 (m, 2H), 5.05-5.27 (m, 2H), 5.80-5.99 (m, 1H), 7.42 (br s, 1H), 7.74-7.98 (m, 4H, ArH); ¹³C NMR (68 MHz, CDCl₃) δ 16.97, 38.01, 38.73, 117.49, 123.79, 129.84, 134.51, 134.84, 164.98, 174.63; EI-MS m/z 258 (M⁺, 7.7), 162 (100), 148 (7.8), 96 (42.9), 69 (76.8). Anal. Calcd for C₁₄H₁₄N₂O₃: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.90; H, 5.42; N, 10.82.

***N*-(1,3-Dioxoisindolin-2-yl)-3,3-dimethylpent-4-enamide (1f)**. Yield 76%, colorless crystals: mp 96-101 °C (EtOAc-hexane); IR (KBr) 3520, 3380, 3170, 2970, 1795, 1730, 1675, 1560, 1415, 1210, 930, 880, 705 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.23 (s, 6H), 2.41 (s, 2H), 5.09 (d, J = 10 Hz, 1H), 5.14 (d, J = 16 Hz, 1H), 6.02 (dd, J = 16, 10 Hz, 1H), 7.72-7.98 (m, 5H); ¹³C NMR (68 MHz, CDCl₃) δ 26.83, 36.41, 46.78, 112.33, 123.82, 129.89, 134.52, 146.66, 165.03, 169.50; EIMS m/z 272 (M⁺, 1.7), 257 (5.2), 242 (4.5), 162 (100), 104 (23.6), 69 (54.6). Anal. Calcd for C₁₅H₁₆N₂O₃: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.21; H, 5.97; N, 10.33.

2-(Cyclopent-2-enyl)-*N*-(1,3-dioxoisindolin-2-yl)acetamide (1g). Yield 89%, colorless crystals: mp 190-192 °C (EtOAc-hexane); IR (KBr) 3250, 1805, 1750, 1670, 1520, 880, 710 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.47-1.63 (m, 1H), 2.10-2.52 (m, 5H), 3.10-3.23 (m, 1H), 5.74-5.86 (m, 2H), 7.74-7.97 (m, 5H); ¹³C NMR (68 MHz, CDCl₃) δ 29.49, 31.85, 39.90, 42.29, 123.95, 129.98, 132.09, 133.28, 134.67, 165.22, 171.01; EIMS m/z 270 (M⁺, 1.8), 204 (35.7), 162 (100), 67 (61.8). Anal. Calcd for C₁₅H₁₄N₂O₃: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.69; H, 5.15; N, 10.34.

Preparation of Methyl 3-endo-(1,3-Dioxoisindolin-2-ylcarbamoyl)bicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (1h). To a solution of *cis*-5-norbornene-endo-2,3-dicarboxylic anhydride (656 mg, 4.00 mmol) in MeOH (10 mL) was added triethylamine (1.0 mL, 8.00 mmol) at rt. After stirring for 10 min,

the solvent was removed *in vacuo* and 10% HCl (10 mL) was added. The acidic mixture was extracted with EtOAc (2 x 50 mL) and the combined organic solvent was washed with brine (2 x 50 mL) and dried over Na₂SO₄. After removal of solvent *in vacuo*, the crude monomethyl ester was used without further purification. EDCI (996 mg, 5.20 mmol) was added to a solution of the crude product and *N*-aminophthalimide (650 mg, 4.00 mmol) in pyridine (20 mL) and the reaction mixture was stirred for 10 h at rt. After the reaction was complete, the mixture was concentrated *in vacuo*, acidified with 10% HCl, and diluted with water (50 mL). The mixture was extracted with EtOAc (2 x 50 mL) and the combined organic solvent was washed with brine (2 x 40 mL), dried over Na₂SO₄, and concentrated. The residue was recrystallized from CH₂Cl₂-hexane to afford the product **1h** (476 mg, 35%). **1h**: colorless crystals, mp 176-178 °C (CH₂Cl₂-hexane); IR (KBr) 3250, 1800, 1745, 1685, 1210, 885, 710 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.44 (dd, *J* = 31, 8.3 Hz, 2H), 3.14 (s, 1H), 3.20-3.35 (m, 2H), 3.45-3.56 (m, 1H), 3.60 (s, 3H), 6.11-6.30 (m, 1H), 6.42-6.62 (m, 1H), 7.66-7.98 (m, 4H), 8.20 (br s, 1H); ¹³C NMR (68 MHz, CDCl₃) δ 19.87, 21.74, 22.33, 23.56, 26.03, 97.99, 104.20, 107.59, 108.73, 111.07, 139.30, 144.98, 147.32; EIMS *m/z* 340 (M⁺, 2.2), 243 (18.7), 179 (27.0), 113 (100). Anal. Calcd for C₁₈H₁₆N₂O₅: C, 63.53; H, 4.74; N, 8.23. Found: C, 63.55; H, 4.52; N, 8.29.

Preparation of *N*-(1,3-Dioxoisindolin-2-yl)-2-vinylbenzamide (1i). An ethereal solution of diazomethane was added dropwise to a solution of phthalaldehydic acid (1.0 g, 6.66 mmol) in EtOAc (10 mL). After removal of solvent *in vacuo*, the residue was purified by short column chromatography using 30% EtOAc-hexane to give the methyl ester (917 mg, 83.9%). The product was converted into the corresponding methyl *o*-allylbenzoate by the Wittig reaction according to the previously reported method.¹⁰ Next, to a solution of the *o*-allylbenzoate (232 mg, 1.432 mmol) in MeOH (5 mL) was added 5% NaOH (20 mL) and the reaction mixture was refluxed for 1 h. After cooling, the mixture was acidified with 10% HCl and extracted with EtOAc (2 x 40 mL). The combined organic solvent was washed with brine (2 x 30 mL), dried over Na₂SO₄, and concentrated. The residue was diluted with pyridine (10 mL). To the solution were added EDCI (394 mg, 1.862 mmol) and *N*-aminophthalimide (385 mg, 2.148 mmol) and the reaction mixture was stirred for 24 h at rt. After the reaction was complete, the solvent was concentrated *in vacuo* and the residue was diluted with EtOAc (70 mL). The organic solution was washed with 10% HCl (2 x 25 mL), 10% Na₂CO₃ (2 x 25 mL), and brine (2 x 30 mL), and dried over Na₂SO₄. After removal of solvent *in vacuo*, the residue was purified by column chromatography on silica gel using 35% EtOAc-hexane to give the product **1i** (134 mg, 32%). **1i**: colorless crystals, mp 172-174 °C (EtOAc-hexane); IR (KBr) 3275, 1790, 1720, 1695, 1265, 1210, 880, 710 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 5.44 (d, *J* = 11 Hz, 1H), 5.78 (d, *J* = 17 Hz, 1H), 7.26 (dd, *J* = 17, 11 Hz, 1H), 7.34 (td, *J* = 7.5, 1.2 Hz, 1H), 7.48 (td, *J* = 7.4, 1.0 Hz, 1H), 7.61 (dd, *J* = 7.9, 0.71 Hz, 1H), 7.69 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.76-8.02 (m, 5H); ¹³C NMR (68 MHz, CDCl₃) δ 117.71, 123.97, 126.38, 127.68, 128.15, 129.97, 130.84,

131.39, 133.91, 134.63, 136.86, 164.92, 167.41; EIMS m/z 292 (M^+ , 11.7), 131 (100), 103 (31.8). Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 70.01; H, 3.98; N, 9.58.

Table 1: Product obtained from compound 1a.

Entry 2.

6-(1,3-Dioxoisindolin-2-yl)-7-oxo-6-azabicyclo[3.2.1]octan-4-yl 2,2,2-Trifluoroacetate (2a): Typical Procedure for Table 1. PIFA (262 mg, 0.722 mmol) was added to a solution of compound **1a** (150 mg, 0.555 mmol) in $CHCl_3$ (10 mL) and the reaction mixture was refluxed for 0.5 h. After the reaction was complete, the solvent was evaporated *in vacuo* and the residue was purified by column chromatography on silica gel using 50% EtOAc-hexane to give the product **2a** (206 mg, 97%). **2a**: colorless oil; IR (neat) 1785, 1730, 1220, 1160, 880, 710 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 1.77-2.44 (m, 4.3H), 2.55-2.81 (m, 1.7H), 2.83-2.90 (m, 0.3H), 2.96-3.15 (m, 0.7H), 3.93-4.00 (m, 0.3H), 4.07 (t, $J = 4.8$ Hz, 0.7H), 5.35 (t, $J = 4.2$ Hz, 0.7H), 5.61-5.70 (m, 0.3H), 7.78-7.98 (m, 4H); EIMS m/z 382 (M^+ , 100), 268 (30.1). HR-EIMS for $C_{17}H_{13}N_2O_5F_3$: 382.0777. Found: 382.0778.

Table 2: Products obtained from compounds 1b-i.

Entry 1.

1-(1,3-Dioxoisindolin-2-yl)-5-oxopyrrolidin-3-yl 2,2,2-Trifluoroacetate (2b): Typical Procedure for Table 2. PIFA (364 mg, 0.848 mmol) was added to a solution of compound **1b** (150 mg, 0.652 mmol) in $CHCl_3$ (10 mL) and the reaction mixture was refluxed for 1 h. After the reaction was complete, the solvent was evaporated *in vacuo* and the residue was purified by column chromatography using 50% EtOAc-hexane to give the product **2b** (125 mg, 56%). **2b**: crystals, mp 169.5-173 °C; IR (KBr) 1790, 1730, 1220, 1160, 1130, 875, 705 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 2.82 (dd, $J = 19, 3.1$ Hz, 1H), 3.15 (dd, $J = 19, 7.8$ Hz, 1H), 3.85 (dd, $J = 11, 2.2$ Hz, 1H), 4.25 (dd, $J = 11, 6.1$ Hz, 1H), 5.65-5.76 (m, 1H), 7.78-8.00 (m, 4H); EIMS m/z 342 (M^+ , 1.1), 228 (100), 175 (34.1), 130 (34.0), 104 (51.2); FABMS m/z 343 ($M^+ + 1$, 100).

Entry 2.

Cyclization of N-(1,3-Dioxoisindolin-2-yl)pent-4-enamide (1c). Following the typical procedure for the cyclization reaction, compound **1c** (150 mg, 0.614 mmol) in $CHCl_3$ (10 mL) was reacted with PIFA (343 mg, 0.798 mmol). After 0.5 h, workup, and column chromatography (50% EtOAc-hexane) gave a mixture of compounds **2c** + **3c** (201 mg, 92%, in a **2c** : **3c** = 3 : 1 ratio, as determined by 1H NMR). **2c** + **3c**: IR (KBr) 1795, 1740, 1720, 1685, 1210, 1175, 880, 710 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 2.00-2.19 (m, 0.75H), 2.30-2.44 (m, 0.40H), 2.46-2.96 (m, 2.85H), 3.91 (dd, $J = 13, 3.0$ Hz, 0.2H), 4.13 (dd, $J = 13, 3.0$ Hz, 0.2H), 4.25-4.47 (m, 1.4H), 4.59 (dd, $J = 11, 2.3$ Hz, 0.7H), 5.49-5.58 (m, 0.2H),

7.76-7.98 (m, 4H); EIMS m/z 356 (M^+ , 0.7), 337 (3.6), 242 (100), 201 (67.3) 130 (33.2).

Entry 3.

Cyclization of *N*-(1,3-Dioxoisindolin-2-yl)-3-methylpent-4-enamide (1d). Following the typical procedure for the cyclization reaction, compound **1d** (150 mg, 0.581 mmol) was reacted with PIFA (325 mg, 0.755 mmol). After 0.5 h, workup and column chromatography (50% EtOAc-hexane) gave a mixture of compounds **2d** + **3d** (200 mg, 93%, in a **2d** : **3d** = 5 : 1 ratio, as determined by ^1H NMR). **2d** + **3d**: IR (KBr) 1800, 1745, 1720, 1215, 1170, 880, 715 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.12-1.45 (m, 3H), 2.18-3.13 (m, 3.3H), 3.46-4.02 (m, 0.6H), 4.08-4.24 (m, 0.5H), 4.34-4.49 (m, 0.7H), 4.64 (td, $J = 12.0$, 3.0 Hz, 0.8H), 5.24-5.32 (m, 0.1H), 7.74-7.98 (m, 4H); EIMS m/z 370 (M^+ , 0.7), 256 (100), 243 (72.3), 215 (40.8).

Entry 4.

Cyclization of *N*-(1,3-Dioxoisindolin-2-yl)-2-methylpent-4-enamide (1e). Following the typical procedure for the cyclization reaction, compound **1e** (150 mg, 0.581 mmol) was reacted with PIFA (325 mg, 0.755 mmol). After 0.5 h, workup and column chromatography (50% EtOAc-hexane) gave a mixture of compounds **2e** + **3e** (194 mg, 90%, in a **2e** : **3e** = 5 : 1 ratio, as determined by ^1H NMR). **2e** + **3e**: IR (KBr) 1795, 1740, 1720, 1680, 1210, 1160, 880, 710 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.32-1.45 (m, 3H), 1.57-1.76 (m, 0.6H), 2.03-3.06 (m, 2.7H), 3.86-4.18 (m, 0.3H), 4.18-4.47 (m, 1.5H), 4.52-4.63 (m, 0.8H), 5.50-5.61 (m, 0.1H), 7.74-7.98 (m, 4H); EIMS m/z 370 (M^+ , 1.3), 256 (100), 243 (37.7), 215 (45.3).

Entry 5.

[1-(1,3-Dioxoisindolin-2-yl)-3,3-dimethyl-5-oxopyrrolidin-2-yl]methyl 2,2,2-Trifluoroacetate (2f). Yield 98%, colorless crystals, mp 114-118.5 $^\circ\text{C}$; IR (KBr) 2970, 1795, 1750, 1710, 1370, 1300, 1210, 1150, 880, 720, 705 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.30 (s, 3H), 1.46 (s, 3H), 2.48 (q, $J = 17.5$ Hz, 2H), 3.88 (dd, $J = 6.4$, 2.6 Hz, 1H), 4.42 (dd, $J = 12$, 6.4 Hz, 1H), 4.66 (dd, $J = 12$, 2.6 Hz, 1H), 7.77-7.99 (m, 4H); EIMS m/z 384 (M^+ , 0.5), 270 (100), 257 (50.0), 229 (12.5), 148 (17.8), 130 (19.9).

Entry 6.

1-*exo*-(1,3-Dioxoisindolin-2-yl)-2-oxooctahydrocyclopenta[*b*]pyrrol-6-yl 2,2,2-Trifluoroacetate (2g). Yield 79%, colorless crystals, mp 203-210 $^\circ\text{C}$; IR (KBr) 1800, 1775, 1740, 1730, 1370, 1220, 1175, 1140, 880, 705 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.75 (m, 1H), 2.00-2.54 (m, 4H), 2.90 (dd, $J = 18.3$, 10.4 Hz, 1H), 3.13-3.30 (m, 1H), 4.29 (d, $J = 7.9$ Hz, 1H), 5.28-5.40 (m, 1H), 7.76-8.08 (m, 4H); EIMS m/z 382 (M^+ , 0.5), 363 (1.5), 268 (100).

Entry 7.

Cyclization of Methyl 3-*endo*-(1,3-Dioxoisindolin-2-ylcarbamoyl)bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate (1h). Following the typical procedure for the cyclization reaction, compound **1h** (150 mg,

0.441 mmol) was reacted with PIFA (246 mg, 0.573 mmol). After 0.5 h, workup and careful column chromatography (85% EtOAc-hexane) gave compounds **2h** (120 mg, 60%) and **2h'** (36 mg, 18%).

Methyl 6-(1,3-Dioxoisindolin-2-yl)-7-oxo-4-*exo*-trifluoroacetoxy-6-azatricyclo[3,2,1,1^{3,8}]nonane-2-*endo*-carboxylate (2h). Oil; IR (neat) 1780, 1840, 1360, 1220, 1160, 880, 710 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.64-1.85 (m, 1H), 2.08 (d, $J = 12$ Hz, 1H), 2.94 (dd, $J = 12, 4.5$ Hz, 1H), 3.05-3.15 (m, 1H), 3.31 (dd, $J = 11, 3.6$ Hz, 1H), 3.50-3.60 (m, 1H), 3.80-3.92 (m, 4H), 5.58 (br s, 1H), 7.74-7.98 (m, 4H); EI-MS m/z 452 (M^+ , 100), 239 (52.0). HR-EIMS for $\text{C}_{20}\text{H}_{15}\text{N}_2\text{O}_7\text{F}_3$: 452.0831. Found: 452.0834.

Methyl 6-(1,3-Dioxoisindolin-2-yl)-7-oxo-4-*endo*-trifluoroacetoxy-6-azatricyclo[3,2,1,1^{3,8}]nonane-2-*endo*-carboxylate (2h'). Oil; IR (neat) 1785, 1740, 1210, 1170, 880, 720 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.55-1.89 (m, 1H), 2.18 (d, $J = 11$ Hz, 1H), 2.83-2.98 (m, 2H), 3.17 (dd, $J = 11, 3.5$ Hz, 1H), 3.29-3.38 (m, 1H), 3.74 (s, 3H), 4.83 (d, $J = 5.1$ Hz, 1H), 5.91 (s, 1H), 7.70 (t, $J = 7.4$ Hz, 1H), 7.80 (t, $J = 7.4$ Hz, 1H), 7.93 (d, $J = 7.4$ Hz, 1H), 8.11 (d, $J = 7.4$ Hz, 1H); EIMS m/z 452 (M^+ , 92.3), 267 (84.7), 239 (100), 113 (77.9). HR-EIMS for $\text{C}_{20}\text{H}_{15}\text{N}_2\text{O}_7\text{F}_3$: 452.0831. Found: 452.0829.

Entry 8.

Cyclization of *N*-(1,3-Dioxoisindolin-2-yl)-2-vinylbenzamide (1i). Following the typical procedure for the cyclization reaction, compound **1i** (150 mg, 0.514 mmol) was reacted with PIFA (343 mg, 0.668 mmol). After 0.5 h, workup and column chromatography (50% EtOAc-hexane) gave compounds **2i** (125 mg, 60%) and **3i** (51 mg, 34%).

2-(1,3-Dioxoisindolin-2-yl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl 2,2,2-Trifluoroacetate (2i). Colorless crystals, mp 156-167 $^\circ\text{C}$; IR (KBr) 1795, 1740, 1730, 1230, 880, 710 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 4.64 (dd, $J = 12, 7.8$ Hz, 1H), 4.84 (dd, $J = 12, 4.0$ Hz, 1H), 5.23 (dd, $J = 7.8, 4.0$ Hz, 1H), 7.50-8.08 (m, 8H); EIMS m/z 404 (M^+ , 0.1), 385 (2.2), 290 (100), 277 (65.7).

2-(1-Oxoisquinolin-2(1*H*)-yl)isoindoline-1,3-dione (3i). Colorless crystals, mp 221-225 $^\circ\text{C}$ (EtOAc); IR (KBr) 1800, 1740, 1680, 1630, 1385, 880, 710 cm^{-1} ; ^1H NMR (270 MHz, acetone- d_6) δ 7.57 (d, $J = 7.6$ Hz, 1H), 8.33 (d, $J = 7.6$ Hz, 1H), 8.40 (d, $J = 8.1$ Hz, 1H), 8.45-8.68 (m, 2H), 8.73-8.95 (m, 4H), 9.09 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (68 MHz, acetone- d_6) δ 107.14, 124.68, 126.47, 127.53, 128.15, 128.39, 130.72, 133.64, 134.21, 136.08, 137.97, 159.56, 164.78; EIMS m/z 290 (M^+ , 90.5), 246 (100), 218 (14.9), 104 (35.1). Anal. Calcd for $\text{C}_{17}\text{H}_{10}\text{N}_2\text{O}_3$: C, 70.34; H, 3.47; N, 9.65. Found: C, 70.11; H, 3.42; N, 9.50.

Table 3: Products **4a**, **4c-i**, and **5c-d** obtained by removal of trifluoroacetyl group under acidic conditions.

Entry 1.

2-(4-Hydroxy-7-oxo-6-azabicyclo[3.2.1]octan-6-yl)isoindoline-1,3-dione (4a): Typical Procedure for Table 4. Compound **2a** (206 mg, 0.539 mmol) in AcOH-THF- H_2O (3 : 1 : 1, 10 mL) was heated at 70 $^\circ\text{C}$

for 30 min. After the reaction was complete, the reaction mixture was diluted with water and extracted with EtOAc (2 x 30 mL). The combined organic solvent was washed with brine (2 x 25 mL), dried over Na₂SO₄, and concentrated. The residue was washed with 50% Et₂O-hexane to give the product **4a** (125 mg, 81%, *endo* : *exo* = 2 : 1, as determined by ¹H NMR). **4a**: colorless crystals, mp 247-250 °C (EtOAc-hexane); IR (KBr) 3370, 1800, 1740, 1700, 1680, 1375, 880, 705 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.40-2.00 (m, 3.5H), 2.11-2.33 (m, 2H), 2.43-2.65 (m, 1.5H, CH₂), 3.73-3.85 (m, 1H), 3.92-4.03 (m, 0.64H), 4.30-4.39 (m, 0.36H), 5.07 (d, *J* = 4.3 Hz, 0.65H), 5.32 (d, *J* = 4.3 Hz, 0.35H), 7.89-8.01 (m, 4H); ¹³C NMR (68 MHz, DMSO-*d*₆) δ 19.41, 21.59, 23.63, 26.21, 30.16, 33.36, 61.54, 61.63, 63.15, 66.09, 123.55, 123.57, 129.21, 129.27, 135.04, 135.09, 164.34, 164.59, 172.28, 173.40; EIMS *m/z* 286 (M⁺, 94.5), 148 (100), 130 (51.8). Anal. Calcd for C₁₅H₁₄N₂O₄: C, 62.93; H, 4.93; N, 9.78. Found: C, 62.86; H, 4.90; N, 9.77.

Entry 2.

2-[2-(Hydroxymethyl)-5-oxopyrrolidin-1-yl]isoindoline-1,3-dione (4c) and 2-(5-Hydroxy-2-oxopiperidin-1-yl)isoindoline-1,3-dione (5c). Following the typical procedure, a mixture of compounds **2c** + **3c** (201 mg, 0.526 mmol) was hydrolyzed in AcOH-THF-H₂O (3 : 1 : 1, 10 mL). After 10 min, workup and column chromatography (30 % acetone-toluene) gave **4c** + **5c** (104 mg, 76%, in a 3 : 1 ratio, as determined by ¹H NMR). After careful chromatography, only small amounts of the pure components **4c** and **5c** could be isolated.

4c: colorless crystals, mp 179-182 °C (EtOAc-hexane); IR (KBr) 3420, 1800, 1740, 1695, 1375, 880, 715 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 2.26-2.48 (m, 2H), 2.50-2.79 (m, 2H), 3.38 (dd, *J* = 11, 3.2 Hz, 1H), 3.55 (td, *J* = 13, 1.6 Hz, 1H), 3.77 (d, *J* = 13 Hz, 1H), 3.90-4.03 (m, 1H), 7.97-8.01 (m, 4H); ¹³C NMR (68 MHz, CDCl₃) δ 19.32, 27.94, 60.47, 61.27, 124.18, 124.25, 129.62, 129.77, 134.90, 135.11, 164.10, 167.17, 173.20; EIMS *m/z* 260 (M⁺, 0.8), 242 (10.9), 229 (100), 201 (93.3). Anal. Calcd for C₁₃H₁₂N₂O₄: C, 60.00; H, 4.65; N, 10.76. Found: C, 59.85; H, 4.63; N, 10.73.

5c: colorless crystals, mp 245-247 °C (EtOAc-hexane); IR (KBr) 3400, 1800, 1740, 1690, 1220, 1120, 1085, 885, 715 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 2.09-2.27 (m, 2H), 2.50 (br s, 1H), 2.62 (dt, *J* = 18, 5.3 Hz, 1H), 2.80-2.98 (m, 1H), 3.66 (ddd, *J* = 11, 3.7, 1.1 Hz, 1H), 3.99 (dd, *J* = 11, 3.7 Hz, 1H), 4.40 (br s, 1H), 7.76-7.99 (m, 4H); ¹³C NMR (68 MHz, DMSO-*d*₆) δ 27.51, 28.02, 57.62, 62.44, 123.55, 123.57, 129.26, 129.34, 135.06, 135.10, 164.10, 164.29, 167.34; EIMS *m/z* 260 (M⁺, 6.1), 242 (16.8), 229 (32.5), 201 (22.2), 175 (100). Anal. Calcd for C₁₃H₁₂N₂O₄: C, 60.00; H, 4.65; N, 10.76. Found: C, 59.81; H, 4.48; N, 10.54.

Entry 3.

2-(5-Hydroxy-2-oxopiperidin-1-yl)isoindoline-1,3-dione (4d) and 2-(5-Hydroxy-4-methyl-2-oxopiperidin-1-yl)isoindoline-1,3-dione (5d). Following the typical procedure, a mixture of compounds

2d + 3d (200 mg, 0.540 mmol) was hydrolyzed in AcOH-THF-H₂O (3 : 1 : 1, 10 mL). After 10 min, workup and column chromatography (30 % acetone-toluene) gave **4d + 5d** (124 mg, 84%, in a 5 : 1 ratio, as determined by ¹H NMR). After careful chromatography, small amounts of the pure components **4d** and **5d** could be isolated.

cis-4d: colorless crystals: mp 164-165 °C (EtOAc-hexane); IR (KBr) 3520, 3460, 2970, 1795, 1750, 1730, 1705, 1360, 1225, 1075, 880, 710 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.34 (d, *J* = 6.8 Hz, 3H), 2.52 (d, *J* = 2.1 Hz, 1H), 2.54 (s, 1H), 2.88-2.99 (m, 1H), 3.63 (dd, *J* = 10, 4.2 Hz, 1H) 3.68-3.83 (m, 3H), 7.81-7.86 (m, 2H), 7.91-7.96 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 14.92, 29.43, 36.30, 59.32, 64.08, 124.16, 124.24, 129.57, 129.85, 134.88, 125.12, 164.45, 167.15, 172.83; EIMS *m/z* 274 (M⁺, 0.2), 256 (5.3), 243 (100). Anal. Calcd for C₁₄H₁₄N₂O₄: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.44; H, 4.94; N, 10.18.

trans-4d: colorless crystals: mp 163-164.5 °C (EtOAc-hexane); IR (KBr) 3480, 1795, 1720, 1470, 1240, 1070, 880, 710 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.29 (d, *J* = 6.8 Hz, 3H), 2.24 (dd, *J* = 17, 6.2 Hz, 1H), 2.76 (dq *J* = 8.9, 6.3 Hz, 1H), 2.83 (dd, *J* = 16.7, 8.3 Hz, 1H), 3.34 (dd, *J* = 11.5, 3.6 Hz, 1H), 3.48 (dt, *J* = 6.3, 2.1 Hz, 1H), 3.62 (ddd, *J* = 13, 12, 2.1 Hz, 1H), 3.74 (ddd, *J* = 14 3.6, 2.1 Hz, 1H), 7.79-7.87 (m, 2H), 7.89-7.97 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 19.26, 27.04, 36.44, 59.55, 68.05, 124.16, 124.24, 129.63, 129.72, 134.89, 135.09, 163.94, 167.17, 172.87; EIMS *m/z* 274 (M⁺, 0.1), 256 (5.1), 243 (100), 215 (31.9). Anal. Calcd for C₁₄H₁₄N₂O₄: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.42; H, 5.01; N, 10.19.

cis- and trans-5d: colorless crystals, mp 229-232 °C (EtOAc-hexane); IR (KBr) 3350, 1795, 1745, 1660, 1220, 1090, 880, 710 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.07 (d, *J* = 6.3 Hz, 3H), 1.97-2.07 (m, 2H), 2.22-2.96 (m, 2H), 3.49 (q, *J* = 5.5 Hz, 1H), 3.90-4.03 (m, 2H), 7.76-7.93 (m, 4H); ¹³C NMR (126 MHz, DMSO-*d*₆) δ 16.72, 33.44, 35.23, 55.54, 67.41, 123.52, 129.25, 129.31, 135.02, 164.10, 164.23, 167.10; EIMS *m/z* 274 (M⁺, 4.3), 256 (11.8), 175 (100), 148 (16.8). Anal. Calcd for C₁₄H₁₄N₂O₄: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.33; H, 4.95; N, 10.21.

Entry 4.

2-(5-(Hydroxymethyl)-3-methyl-2-oxopyrrolidin-1-yl)isoindoline-1,3-dione (4e) and 2-(5-Hydroxy-3-methyl-2-oxopiperidin-1-yl)isoindoline-1,3-dione (5e). Following the typical procedure, a mixture of compounds **2e + 3e** (194 mg, 0.524 mmol) was hydrolyzed in AcOH-THF-H₂O (3 : 1 : 1, 10 mL). After 10 min, workup and column chromatography (30 % acetone-toluene) gave **4e + 5e** (122 mg, 85%, in a 6 : 1 ratio, as determined by ¹H NMR). After careful chromatography, small amounts of the pure components **4e** and **5e** could be isolated.

cis- and trans-4e: colorless crystals: mp 141-148 °C (EtOAc-hexane); IR (KBr) 3450, 1795, 1740, 1705, 1225, 885, 710 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 1.34 (d, *J* = 7.1 Hz, 0.5H), 1.35 (d, *J* = 7.1 Hz, 2.5H), 2.00-2.15 (m, 1H), 2.36-2.59 (m, 1H), 2.69-2.90 (m, 1H), 3.30 (dd, *J* = 12, 2.6 Hz, 0.7H), 3.38 (dd, *J* = 12,

3.2 Hz, 0.3H), 3.50-3.61 (m, 1H), 3.73-3.80 (m, 1H), 3.90 (t, $J = 6.4$ Hz, 1H), 7.80-7.96 (m, 4H); ^{13}C NMR (68 MHz, CDCl_3) δ 16.12, 17.05, 27.18, 29.03, 33.82, 34.22, 59.12, 59.25, 59.88, 61.72, 124.16, 124.22, 129.66, 129.72, 134.89, 135.07, 163.96, 167.24, 175.96; EIMS m/z 274 (M^+ , 1.1), 256 (10.1), 243 (100), 215 (56.1). Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.38; H, 5.07; N, 10.13.

cis- and trans- 5e: colorless crystals: mp 229-232 °C (EtOAc-hexane); IR (KBr) 3440, 1790, 1740, 1680, 1650, 1210, 880, 710 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.21-1.41 (m, 3H), 1.75-2.10 (m, 1.3H), 2.16-2.30 (m, 0.7H), 2.35-2.47 (m, 0.4H), 2.57-2.93 (m, 1.1H), 2.96-3.13 (m, 0.6H), 3.60-3.72 (m, 1.0H), 3.95 (ddd, $J = 12, 4.7, 1.0$ Hz, 0.4H), 4.05 (dd, $J = 12, 4.7$ Hz, 0.6H), 4.39 (br s, 0.9H), 7.73-7.98 (m, 4H, ArH); ^{13}C NMR (68 MHz, CDCl_3) δ 16.69, 16.78, 31.79, 34.15, 36.10, 38.58, 57.97, 58.85, 63.43, 64.69, 123.87, 123.93, 123.96, 129.79, 129.85, 129.88, 129.99, 134.64, 134.74, 164.60, 164.81, 165.12, 171.20, 171.45; EIMS m/z 274 (M^+ , 5.8), 256 (8.6), 175 (100), 130 (26.1). Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.36; H, 4.90; N, 10.05.

Entry 5.

2-[2-(Hydroxymethyl)-3,3-dimethyl-5-oxopyrrolidin-1-yl]isoindoline-1,3-dione (4f). Yield 76%, colorless crystals, mp 143-144 °C (EtOAc-hexane); IR (KBr) 3510, 2980, 1795, 1740, 1390, 1300, 1210, 1080, 880, 710 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.34 (s, 3H), 1.41 (s, 3H), 2.19 (d, $J = 17$ Hz, 1H), 2.71 (d, $J = 17$ Hz, 1H), 3.30-3.39 (m, 1H), 3.53 (dd, $J = 11, 5.7$ Hz, 1H), 3.65-3.88 (m, 2H, 7.78-8.00 (m, 4H, ArH); ^{13}C NMR (68 MHz, CDCl_3) δ 23.41, 30.63, 35.33, 43.28, 59.73, 70.51, 124.11, 124.21, 129.61, 129.87, 134.85, 135.09, 164.41, 167.13, 172.33; EIMS m/z 288 (M^+ , 0.2), 257 (100), 229 (16.1), 148 (22.2), 130 (23.1). Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.47; H, 5.55; N, 9.74.

Entry 6.

2-(6-*exo*-Hydroxy-2-oxohexahydrocyclopenta[*b*]pyrrol-1(2*H*)-yl)isoindoline-1,3-dione (4g). Yield 87%, colorless crystals, mp 231-233 °C (EtOAc-hexane); IR (KBr) 3370, 1785, 1730, 1695, 1360, 880, 710 cm^{-1} ; ^1H NMR (270 MHz, $\text{DMSO-}d_6$) δ 1.42 (m, 2H), 1.84-2.20 (m, 2H), 2.26 (dd, $J = 18, 3.5$ Hz, 1H), 2.78 (dd, $J = 11, 18$ Hz, 1H), 2.92-3.13 (m, 1H), 3.98 (d, $J = 7.9$ Hz, 1H), 4.07 (d, $J = 3.1$ Hz, 1H), 4.81 (d, $J = 3.5$ Hz, 1H), 7.92-8.14 (m, 4H, ArH); ^{13}C NMR (68 MHz, $\text{DMSO-}d_6$) δ 30.90, 31.60, 32.15, 34.15, 70.66, 73.70, 123.88, 124.00, 129.16, 129.33, 135.49, 135.55, 164.54, 164.80, 172.29; EIMS m/z 286 (M^+ , 2.2), 268 (100), 162 (12.4), 148 (43.7), 104 (46.3), 76 (38.6). Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.87; H, 4.81; N, 9.68.

Entry 7.

Methyl 6-(1,3-Dioxoisoindolin-2-yl)-7-oxo-4-*exo*-hydroxy-6-azatricyclo[3,2,1, $1^{3,8}$]nonane-2-*endo*-carboxylate (4h). Yield 68%, colorless crystals, mp 194-196 °C (EtOAc): IR (KBr) 3510, 1790, 1730,

1695, 880, 705 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.57 (d, $J = 11$ Hz, 1H), 2.16 (d, $J = 11$ Hz, 1H), 2.26-2.40 (m, 1H), 2.73-2.92 (m, 2H), 3.17 (dd, $J = 11, 3.9$ Hz, 1H), 3.40-3.53 (m, 1H), 3.69 (d, $J = 5.1$ Hz, 1H), 3.75 (s, 3H), 4.59 (br s, 1H), 7.72-7.95 (m, 4H); ^{13}C NMR (68 MHz, CDCl_3) δ 32.42, 41.30, 47.52, 48.27, 52.11, 68.80, 72.54, 123.80, 123.93, 129.77, 129.79, 134.57, 134.63, 163.73, 164.29, 170.27, 172.55; EIMS m/z 356 (M^+ , 9.8), 328 (80.4), 229 (100), 210 (56.1), 122 (72.3). Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.54; H, 4.36; N, 7.64.

Entry 8.

2-(4-Hydroxy-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)isoindoline-1,3-dione (4i). Yield 83%, colorless crystals, mp 215-218 $^\circ\text{C}$ (EtOAc-hexane); IR (KBr) 3515, 1795, 1745, 1730 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 3.34 (t, $J = 7.0$ Hz, 1H), 4.05-4.23 (m, 2H), 4.90 (s, 1H), 7.56 (t, $J = 6.8$ Hz, 2H), 7.71 (t, $J = 7.8$ Hz, 1H), 7.80-8.07 (m, 5H); ^{13}C NMR (68 MHz, CDCl_3) δ 60.45, 63.66, 122.39, 124.25, 124.35, 124.49, 128.75, 129.17, 129.83, 129.87, 133.12, 134.99, 135.18, 142.00; 164.49, 166.12, 167.16; EIMS m/z (M^+ , 0.3), 278 (100). Anal. Calcd for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_4$: C, 66.23; H, 3.92; N, 9.09. Found: C, 66.07; H, 3.85; N, 8.94.

Table 4: Products 6a, 6c, and 6d obtained by removal of phthaloyl group.

Entry 1.

6-Amino-4-hydroxy-6-azabicyclo[3.2.1]octan-7-one (6a): Typical Procedure for Table 4. A solution of compound **2a** (200 mg, 0.523 mmol) and hydrazine monohydrate (105 mg, 2.615 mmol) in EtOH (5 mL) was heated at 100 $^\circ\text{C}$ for 0.5 h. After the reaction was complete, the solvent was concentrated *in vacuo*. Insoluble phthaloyl hydrazide was removed by filtration and washed with toluene. The filtrate was concentrated *in vacuo* and the residue was purified by short column chromatography using 20% MeOH-EtOAc to give the product **6a** (72 mg, 88%). **6a**: colorless crystals, mp 174-177 $^\circ\text{C}$ (EtOAc); IR (KBr) 3300, 1650, 1420, 1235, 1085, 1040, 965 cm^{-1} ; ^1H NMR (270 MHz, $\text{DMSO}-d_6$) δ 1.16-1.29 (m, 0.5H), 1.34-1.82 (m, 4.5H), 1.92-2.11 (m, 1H), 2.23 (br s, 0.6H), 2.29 (br s, 0.4H), 3.38-3.52 (m, 1H), 3.89-4.03 (m, 1H), 4.53 (s, 1.3H), 4.75 (s, 0.7H), 4.89 (d, $J = 4.1$ Hz, 0.7H), 5.06 (dd, $J = 4.1$ Hz, 0.3H); ^{13}C NMR (68 MHz, DMSO) δ 18.96, 22.10, 23.95, 26.55, 27.55, 33.45, 37.95, 38.58, 61.88, 61.92, 62.07, 66.22, 172.48, 174.33; EIMS m/z 156 (M^+ , 100), 140 (84.8), 122 (25.4), 84 (87.8). Anal. Calcd for $\text{C}_7\text{H}_{12}\text{N}_2\text{O}_2$: C, 53.83; H, 7.74; N, 17.94. Found: C, 53.71; H, 7.51; N, 17.72.

Entry 2.

1-Amino-5-(hydroxymethyl)pyrrolidin-2-one (6c). Yield 73%, oil, IR (neat) 3300, 1670, 1420, 1290 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.68-1.83 (m, 1H), 2.01-2.18 (m, 1H), 2.29-2.52 (m, 2H), 3.33 (br s, 1H), 3.60-3.84 (m, 2H), 3.85-3.97 (m, 1H), 4.12 (br s, 2H); ^{13}C NMR (68 MHz, CDCl_3) δ 18.71, 28.70, 61.40, 62.31, 174.32; EI-MS m/z 130 (M^+ , 13.0), 99 (100), 84 (1.8), 57 (46.3); HR-EIMS for $\text{C}_5\text{H}_{10}\text{N}_2\text{O}_3$.

130.0742. Found: 130.0748.

Entry 3.

1-Amino-5-(hydroxymethyl)-4,4-dimethylpyrrolidin-2-one (6f). Yield 88%, yellow crystals, mp 125-127 °C (EtOAc-hexane); IR (KBr) 3300, 1680, 1080, 990 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.06 (s, 3H), 1.19 (s, 3H), 2.21 (dd, $J = 27, 17$ Hz, 2H), 3.36 (dd, $J = 6.5, 2.4$ Hz, 1H), 3.42-3.56 (m, 1H), 3.72-3.94 (m, 2H), 4.16 (s, 2H); ^{13}C NMR (68 MHz, CDCl_3) δ 23.01, 29.44, 33.70, 44.69, 60.50, 70.98, 174.00; EIMS m/z 158 (M^+ , 9.4), 127 (100), 111 (0.8), 85 (69.3). Anal. Calcd for $\text{C}_7\text{H}_{14}\text{N}_2\text{O}_2$: C, 53.15; H, 8.92; N, 17.71. Found: C, 53.26; H, 8.90; N, 17.53.

REFERENCES AND NOTES

1. M. Kawase, T. Kitamura, and Y. Kikugawa, *J. Org. Chem.*, 1989, **54**, 3394.
2. Y. Kikugawa, A. Nagashima, T. Sakamoto, E. Miyazawa, and M. Shiiya, *J. Org. Chem.*, 2003, **68**, 6739.
3. Y. Kikugawa and M. Kawase, *Chem. Lett.*, 1990, 581.
4. K. Murata, M. Tsukamoto, T. Sakamoto, S. Saito, and Y. Kikugawa, *Synthesis*, 2008, 32.
5. P. G. Gassman, F. Hoyda, and J. Dygos, *J. Am. Chem. Soc.*, 1968, **90**, 2716; P. G. Gassman and J. Dygos, *Tetrahedron Lett.*, 1970, 4745.
6. (a) A. Correa, I. Tellitu, E. Domínguez, and R. SanMartín, *J. Org. Chem.*, 2006, **71**, 8316. (b) S. Serena, I. Tellitu, E. Domínguez, I. Moreno, and R. SanMartín, *Tetrahedron*, 2004, **60**, 6533. (c) S. Serena, I. Tellitu, E. Domínguez, I. Moreno, and R. SanMartín, *Tetrahedron Lett.*, 2003, **44**, 3483.
7. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.
8. An aziridinium ion intermediate is assumed in a similar PIFA promoted olefin amidohydroxylation: see ref. 6a-c.
9. J. W. Bastable, J. D. Hobson, and W. D. Riddell, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2205.
10. R. A. V. Rama, R. D. Reddeppa, and R. B. Venkateswara, *Indian J. Chem., Sect. B*, 1988, **27B**, 1065.