JOC*Note*

Steric Hindrance-Controlled Pd(0)-Catalyzed Coupling−Cyclization of 2,3-Allenamides and Organic Iodides. An Efficient Synthesis of Iminolactones and γ-Hydroxy-γ-lactams

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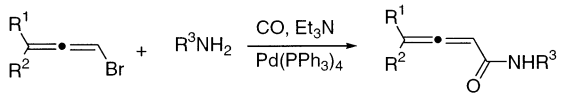
Abstract: Under the catalysis of 1 mol % $Pd(PPh_3)_4$, the reaction of 4,4-disubstituted 2,3-allenamides and organic iodides in toluene afforded iminolactones stereospecifically in >90% yields using K_2CO_3 (2 equiv)−5 mol % TBAB as the base. A similar reaction with 4-monosubstituted 2,3-allenamides afforded γ-hydroxy-γ-lactams in relatively lower yields. The N/O-attack selectivity may be determined by the steric effect at the 4-position of 2,3-allenamides.

Recently, much of the attention of our research group has been paid to the chemistry of allenes.[1] The coupling−cyclization reaction of functionalized allenes provides new methodologies for the synthesis of carbocycles[2] and heterocycles such as furans,[3] 2,5-dihydrofurans,[4] oxiranes,[5] and butenolides.[6] With the chemistry of 2,3-allenoic acids[6] and esters,[7] we envisioned that Pd(0)-catalyzed coupling−cyclization reaction of 2,3-allenamides with organic iodides would provide a new synthetic pathway to pyrrol-2(5*H*)-ones and 5-hydroxypyrrol-2(5*H*)-ones, a class of compounds of biological interest.

In 2000, we developed an efficient methodology for the synthesis of 4-halo-5-hydroxypyrrol-2(5*H*)-ones via the cyclization reaction of 2,3-allenamides with CuX_2.[8] In this paper, we report our recent results on the Pd(0)-catalyzed coupling−cyclization of 2,3-allenamides and organic iodides.

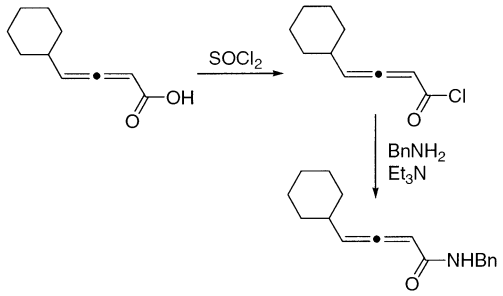
Synthesis of Starting Material. 2,3-Allenamides **1a**,**e**−**g** were prepared by the palladium-catalyzed carbonylation of 1,2-allenic bromide in the presence of amines (Scheme 1).[9]

SCHEME 1



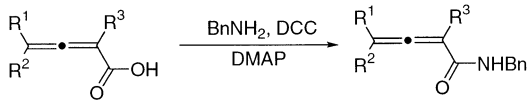
R^1 = *n*-Bu, R^2 = H, R^3 = Bn **1a** (42 %)
R^1 = R^2 = Me, R^3 = Bn **1e** (85 %)
R^1 = R^2 = Me, R^3 = *n*-Bu **1f** (84 %)
R^1 = R^2 = Me, R^3 = H **1g** (77 %)

SCHEME 2



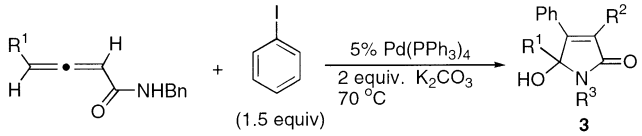
1b (57 %)

SCHEME 3



R^1, R^2 = $(CH_2)_5$, R^3 = *n*-Pr **1c** (74 %)
R^1 = R^2= Me, R^3 = Bn **1d** (55 %)
R^1 = R^2 = R^3 = Me **1h** (45 %)

SCHEME 4



1a R^1 = *n*-Bu	DMF	9 h	**3a** (45%)
1b R^1 = *c*-hexyl	toluene	30 h	**3b** (48%)

2,3-Allenamide **1b** was prepared by the aminolysis of the corresponding of 2,3-allenoyl chloride (Scheme 2).[10]

2,3-Allenamides **1c**,**d**,**h** were prepared by the DMAP-catalyzed amidation of the corresponding 2,3-allenoic acids with amines (Scheme 3).

Pd(0)-Catalyzed Coupling−Cyclization of 2,3-Allenamides and Organic Halides. We initiated this study with 4-monosubstituted 2,3-allenamides **1a** and **1b**. The coupling−lactamization reaction with PhI in DMF or toluene under the catalysis of $Pd(PPh_3)_4$ was followed by γ-hydroxylation[8] to afford 5-hydroxypyrrolin-2(5*H*)-ones **3a** and **3b** in 45 and 48% yields, respectively (Scheme 4). The structures of these two products were determined by the X-ray diffraction study of **3b**.[11]

However, it is surprising to observe that both 2.5 mol % $Pd_2(dba)_3$•$CHCl_3$−10 mol % PPh_3 and 5 mol % Pd-

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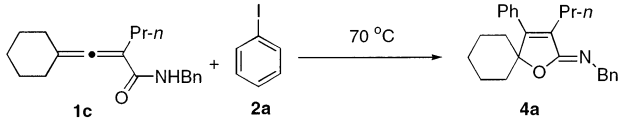
TABLE 1. Pd(0)-Catalyzed Coupling−Cyclization Reaction of 1a with PhI under Different Conditions



1c 2a 4a

entry	catalyst (mol %)[a]	Ag_2CO_3 (mol %)	TBAB (mol %)	K_2CO_3 (equiv)	PhI (equiv)	solvent	time (h)	yield of **4a** (%)
1	A	5	10	4	1.3	toluene	18.5	99
2	B (5)	none	10	4	1.3	toluene	18	99
3	B (5)	none	none	4	1.3	CH_3CN	17	92
4	B (5)	none	none	4	1.3	THF[b]	17	88
5	B (5)	none	none	4	1.3	DMF	17	92
6	C (1)[c]	none	5	2	1.1	toluene	4 days	67
7	B (1)	none	5	2	1.1	toluene	47	95

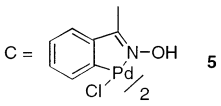
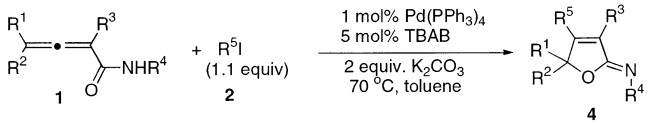
[a] A = 2.5 mol % $Pd_2(dba)_3$·$CHCl_3$, 10 mol % PPh_3; B = $Pd(PPh_3)_4$. [b] Reflux. [c] C =  **5**

TABLE 2. Pd(0)-Catalyzed Synthesis of Iminolactones[a]



	1				2	time	yield of **4**
entry	R^1	R^2	R^3	R^4	R^5	(h)	(%)
1	$(CH_2)_5$		*n*-Pr	Bn (**1c**)	Ph (**2a**)	47	95 (**4a**)
2	$(CH_2)_5$		*n*-Pr	Bn (**1c**)	*p*-MeC_6H_4 (**2b**)	47	95 (**4b**)
3	$(CH_2)_5$		*n*-Pr	Bn (**1c**)	*p*-$MeOC_6H_4$ (**2c**)	65	95 (**4c**)
4	$(CH_2)_5$		*n*-Pr	Bn (**1c**)	*p*-$NO_2C_6H_4$ (**2d**)	72	94 (**4d**)
5	$(CH_2)_5$		*n*-Pr	Bn (**1c**)	*p*-$MeO_2CC_6H_4$ (**2d**)	44	100 (**4e**)
6	Me	Me	Bn	Bn (**1d**)	Ph (**2a**)	65	96 (**4f**)
7	Me	Me	Bn	Bn (**1d**)	*p*-MeC_6H_4 (**2b**)	48	92 (**4g**)
8	Me	Me	Bn	Bn (**1d**)	*p*-$MeOC_6H_4$ (**2c**)	65	93 (**4h**)
9	Me	Me	Bn	Bn (**1d**)	*p*-$NO_2C_6H_4$ (**2d**)	72	94 (**4i**)
10	Me	Me	Bn	Bn (**1d**)	*p*-$MeO_2CC_6H_4$ (**2d**)	72	96 (**4j**)
11	Me	Me	H	Bn (**1e**)	Ph (**2a**)	22	90 (**4k**)
12	Me	Me	H	Bu (**1f**)	Ph (**2a**)	24	91 (**4l**)
13	Me	Me	H	H (**1g**)	*p*-MeC_6H_4 (**2b**)	22	94 (**4m**)
14	Me	Me	H	H (**1g**)	*p*-$MeOC_6H_4$ (**2c**)	22	93 (**4n**)
15	Me	Me	H	H (**1g**)	*p*-$MeO_2CC_6H_4$ (**2d**)	22	90 (**4o**)
16[b]	Me	Me	Me	Bn (**1h**)	(*E*)-1-hexenyl	17	75 (**4p**)
17[b]	Me	Me	Me	Bn (**1h**)	(*Z*)-2-MeO_2CCH=CH	20	99 (**4q**)
18[b]	Me	Me	Me	Bn (**1h**)	(*E*)-2-MeO_2CCH=CH	20	99 (**4r**)

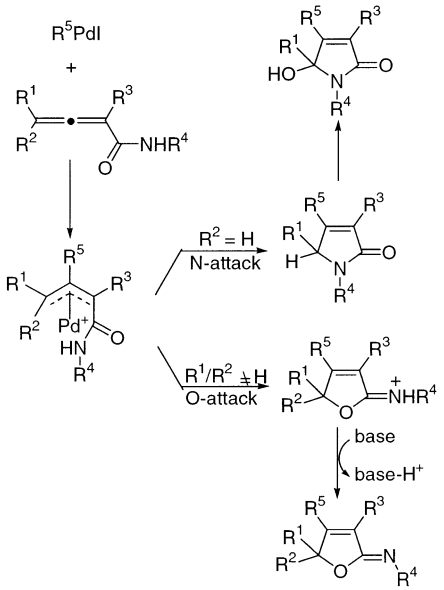
[a] Reaction was carried out using 0.25 mmol of **1** and **2** (1.1 equiv) in 2 mL of toluene. [b] 5% $Pd(PPh_3)_4$ and 1.5 equiv of R^5I were used.

$(PPh_3)_4$ can catalyze the reaction of 2,3-allenamides **1c** with PhI to afford the unexpected iminolactone **4a** in 99% yield (entries 1 and 2, Table 1). The corresponding reactions in MeCN, THF, and DMF in the presence of K_2CO_3 gave **4a** in slightly lower yields (entries 3−5, Table 1). Finally, it was observed that the reaction with *1 mol % Pd(PPh3)4* in toluene using K_2CO_3 (2 equiv)−5 mol % TBAB (tetra(*n*-butyl) amonium bromide) as the base (defined as conditions A) afforded the product **4a** in 95% yield after 47 h (entry 7, Table 1). With 1 mol % catalyst, the reaction with TBAB worked somewhat more cleanly. With cyclic palladium complex **5** as the catalyst, the yield of **4a** dropped to 67% (entry 6, Table 1).

With conditions A as the standard conditions, the reaction went smoothly to give products **4** in excellent yields. Some of the typical results are summarized in Table 2. From the results shown in Table 2, the following points are noteworthy. (1) The structures of the iminolactones were unambiguously determined by the X-ray diffraction studies of products **4f** and **4o**.[12] Only the stereoisomer with R^4 orientated toward the cyclic oxygen was formed, which may be attributed to the steric hindrance between R^3 and R^4. (2) In most cases, 1 mol % $Pd(PPh_3)_4$ is sufficient to provide the products **4** in excellent yields. (3) The R^4 group can be Bn, *n*-Bu, or H. (4) R^3 can be an Bn, H, or an alkyl group. (5) Both electron-deficient and electron-rich aryl halides can be

(11) CCDC 178889. Crystal Data for **3b**: $C_{23}H_{25}NO_2$, MW = 347.44, monoclinic, space group *P*2(1)/*n*, Mo Kα, final *R* indices [$I > 2\sigma(I)$], R_1 = 0.0374, wR_2 = 0.0675, a = 11.0641(10) Å, b = 6.5484(6) Å, c = 26.977(3) Å, α = 90°, β = 93.537(2)°, γ = 90°, T = 293(2) K, Z = 4, reflections collected/unique: 11472/4586 (R_{int} = 0.0510), no observation [$I > 2\sigma(I)$] 2001, parameters 335.

SCHEME 5



applied. (6) The reaction of 4,4-disubstituted 2,3-allenamides with 1-alkenyl iodides also afforded the corresponding iminolactams in good to excellent yields. The configurations of the C=C bond in 1-alkenyl iodides remained intact (entries 16−18, Table 2).

From this study, it is interesting to observe that in the reaction of 4,4-disubstituted-2,3-allenamides, the nucleophilicity of the carbonyl oxygen is much higher than that of the amido nitrogen atom. The reaction is believed to proceed via a mechansim consisting of an oxidative addition reaction, a π-allyl palladium intermediate-forming carbopalladation reaction, and an exclusive intramolecular nucleophilic attack of the carbonyl oxygen followed by the loss of H^+; this generates the C=N bond to afford iminolactones[11−13] (for 4,4-disubstituted 2,3-allenamides) or intramoleculer nucleophilic attack of the nitrogen atom to form γ-lactams, which can be further oxidized to γ-hydroxy-γ-lactams (for 4-monosubstituted 2,3-allenamides) (Scheme 2). The N−/O− attack selectivity may be attributed to the steric hindrance at the 4-positions of 2,3-allenamides. They were synthesized from the aminolysis of thionophthalides[13] and cyclization of γ-hydroxy-nitriles[14] or -oxazolines.[15] Due to the generality, high yield, diversity, and highly setereoselective nature of this reaction, it will show its potential in organic synthesis.

(12) CCDC 178890 and 178891. Crystal Data for **4f**: $C_{26}H_{25}NO$, MW = 367.47, monoclinic, space group *P*2(1)/*c*, Mo Kα, final *R* indices [$I > 2\sigma(I)$], $R_1 = 0.0875$, w$R_2 = 0.1686$, $a = 18.289(6)$ Å, $b = 11.795(4)$ Å, $c = 19.888(7)$ Å, $\alpha = 90°$, $\beta = 101.744(5)°$, $\gamma = 90°$, $T = 293(2)$ K, $Z = 8$, reflections collected/unique: 20293/7365 ($R_{int} = 0.2424$), no observation [$I > 2\sigma(I)$] 849, parameters 509. Crystal Data for **4o**: $C_{14}H_{15}NO_3$, MW = 245.27, orthorhombic, space group *Pnma*, Mo Kα, final *R* indices [$I > 2\sigma(I)$], $R_1 = 0.0386$, w$R_2 = 0.0772$, $a = 13.8655(14)$ Å, $b = 7.1721(7)$ Å, $c = 12.5108(12)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $T = 293(2)$ K, $Z = 4$, reflections collected/unique: 7316/1606 ($R_{int} = 0.0508$), no observation [$I > 2\sigma(I)$] 861, parameters 144.

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Experimental Section

Synthesis of 1a,e−g: General Procedure. A stainless steel autoclave (250 mL) fitted with a glass reactor with a stirring bar inside was charged with THF (50 mL), 1,2-allenyl bromide (27.8 mmol), Et_3N (30.6 mmol), and $Pd(PPh_3)_4$ (0.28 mmol) sequentially. The autoclave was charged with CO with a pressure of 25 atm. After the mixture was stirred for 2 h at rt, CO was released. The reaction was quenched with water followed by the addition of CH_2Cl_2. After separation, the organic phase was washed sequentially with 1 N HCl and brine. After evaporation, the residue was purified by flash chromatography on silica gel to afford allenamides **1a**,**e**−**g**.

***N*-Benzyl Octa-2,3-dienamide (1a):** white solid, mp 70−72 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.24 (m, 5H), 6.18 (bs, 1H), 5.63−5.56 (m, 2H), 4.47 (d, $J = 5.7$ Hz, 2H), 2.15−2.07 (m, 2H), 1.45−1.28 (m, 4H), 0.87 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 207.48, 165.12, 138.27, 128.58, 127.57, 127.36, 96.90, 91.20, 43.52, 30.77, 27.53, 22.06, 13.69; MS *m*/*z* 229 (M^+, 1.78), 91 (100); IR (KBr) 3268, 1960, 1628 cm^{-1}; Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11 Found: C, 78.45; H, 8.49; N, 5.92.

Synthesis of 1b. In a dry flask containing 4-cyclohexylbuta-2,3-dienoic acid (833 mg, 5 mmol) was added $SOCl_2$ (1 mL, 14 mmol). After stirring for 30 min at rt, the excess $SOCl_2$ was removed under reduced pressure to afford 4-cyclohexylbuta-2,3-dienoyl chloride, which was dissolved in dry ether (10 mL) for conversion in the next step.

To a mixture of benzylamine (0.6 mL, 5.5 mmol) and Et_3N (0.78 mL, 5.5 mmol) in dry ether (20 mL) was added 4-cyclohexylbuta-2, 3-dienoyl chloride in dry ether dropwise at rt. After the mixture was stirred for 3 h, the precipitate was removed by filtration and the solvent was evaporated to afford the residue, which was purified by flash chromatography on silica gel to afford 732 mg (57%) of ***N*-Benzyl 4-cyclohexylbuta-2,3-dienamide (1b)**: white solid, mp 118−120 °C (petroleum ether/diethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.23 (m, 5H), 6.20 (bs, 1H), 5.67−5.58 (m, 2H), 4.47 (d, $J = 5.7$ Hz, 2H), 2.15−2.08 (m, 1H), 1.79−1.61 (m, 5H), 1.34−1.06 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 206.68, 165.15, 138.32, 128.55, 127.46, 127.31, 102.66, 92.04, 43.45, 36.79, 32.78, 32.65, 25.77, 25.71, 25.70; MS *m*/*z* 255 (M^+, 20.67), 91 (100); IR (KBr) 3281, 1958, 1628 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.95; H, 8.39; N, 5.33.

Synthesis of 1c,d,h. To a 50 mL dry flask containing allenoic acid (5.25 mmol) and dry CH_2Cl_2 (10 mL) were added sequentially a solution of DCC (5.5 mmol) and DMAP (0.26 mmol) in dry CH_2Cl_2 (5 mL) and a solution of benzylamine (5.8 mmol) in dry CH_2Cl_2 (5 mL) at −30 °C. After the mixture was stirred at room temperature for 6 h, the precipitate was removed by filtration. After evaporation, the residue was purified by flash chromatography on silica gel to afford allenamides **1c**,**d**,**h**.

***N*-Benzyl 3-Cyclohexylidene-2-propylacrylamide (1c):** white solid, mp 63−65 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 6.21 (bs, 1H), 4.48 (d, $J = 5.7$ Hz, 2H), 2.26 (t, $J = 7.5$ Hz, 2H), 2.18−2.15 (m, 4H), 1.59−1.41 (m, 8H), 0.93 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 198.98, 167.33, 138.83, 128.59, 127.35, 127.22, 108.94, 100.86, 43.54, 31.06, 29.78, 27.56, 25.81, 21.25, 13.64; MS *m*/*z* 283 (M^+, 38.18), 91 (100); IR (KBr) 3324, 1954, 1637 cm^{-1}. Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.37; H, 9.16; N, 4.67.

1-Benzyl-5-butyl-5-hydroxy-4-phenylpyrrol-2(5*H*)-one (3a). To a mixture of potassium carbonate (97 mg, 0.70 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) in DMF (2 mL) were added allenamide **1a** (80 mg, 0.35 mmol) and iodobenzene (60 μL, 0.53 mmol) sequentially under Ar. After the mixture was stirred at 70 °C for 9 h, water was added and the reaction mixture was extracted with ether. The organic layer was washed with brine and dried over anhydrous sodium sulfate. After evaporation, the residue was purified by flash chromatography on silica gel to afford 50 mg (45%) of **3a**: white solid, mp 178−180 °C (*n*-hexane−CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.66 (m, 2H), 7.38−7.13 (m, 8H), 6.18 (s, 1H), 4.59 (d, $J = 15.4$ Hz, 1H),

4.38 (d, J = 15.0 Hz, 1H), 3.62 (bs, 1H), 1.80−1.72 (m, 2H), 0.78−0.36 (m, 7H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.89, 158.96, 138.65, 131.22, 130.37, 129.07, 128.86, 128.66, 127.68, 127.58, 121.07, 94.56, 41.95, 34.95, 25.08, 22.13, 13.76; MS m/z 321 (M^+, 3.42), 91 (100); IR (KBr) 3120, 1675 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.53; H, 7.34; N, 4.32.

1-Benzyl-5-*c*-hexyl-5-hydroxy-4-phenylpyrrol-2(5*H*)-one (3b). To a mixture of potassium carbonate (83 mg, 0.60 mmol), TBAB (5 mg, 0.016 mmol), and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) in toluene (2 mL) were added allenamide **1b** (77 mg, 0.30 mmol) and iodobenzene (52 μL, 0.45 mmol) sequentially under Ar. The resulting mixture was heated to 70 °C for 30 h to afford 50 mg (48%) of **3b**: white solid, mp 198−200 °C (*n*-hexane−CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61−7.58 (m, 2H), 7.35−7.12 (m, 8H), 5.96 (s, 1H), 4.57 (d, J = 15.4 Hz, 1H), 4.37 (d, J = 15.4 Hz, 1H), 4.06 (bs, 1H), 1.73−1.28 (m, 6H), 0.82−0.42 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.75, 160.91, 138.57, 133.69, 129.87, 128.77, 128.68, 128.54, 128.14, 127.34, 122.83, 96.71, 44.11, 42.49, 27.16, 26.84, 26.72, 26.12, 26.07; MS m/z 347 (M^+, 9.15), 91 (100); IR (KBr) 3270, 1665 cm^{-1}. Anal. Calcd for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.20; H, 7.26; N, 3.67.

Pd(0)-Catalyzed Coupling−Cyclization of 2,3-Allenamides and Aryl Iodides. Typical Procedure for Synthesis of 4a. To a mixture of potassium carbonate (68 mg, 0.49 mmol), TBAB (4 mg, 0.012 mmol), and $Pd(PPh_3)_4$ (3 mg, 0.0026 mmol) in toluene (2 mL) were added allenamide **1c** (70 mg, 0.25 mmol) and iodobenzene (32 μL, 0.28 mmol) sequentially under Ar. The resulting mixture was heated to 70 °C for 47 h. After evaporation, the residue was purified by flash chromatography on silica gel to afford 84 mg (95%) of **4a**:

***N*-Benzyl (4-Phenyl-3-propyl-1-oxa-spiro[4,5]dec-3-enylidene) Amine (4a):** light yellow solid, mp 71.5−72 °C (*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.03 (m, 10H), 4.61 (s, 2H), 2.06 (t, J = 7.7 Hz, 2H), 1.64−1.35 (m, 11H), 1.05−090 (m, 1H), 0.72 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 163.69, 158.16, 141.84, 134.07, 131.41, 128.62, 128.57, 128.33, 128.21, 127.94, 126.33, 89.93, 51.20, 34.44, 26.39, 24.86, 22.38, 21.87, 14.20; MS m/z 359 (M^+, 93.68), 358 (100); IR (KBr) 1681 cm^{-1}. Anal. Calcd for $C_{25}H_{29}NO$: C, 83.52; H, 8.13; N, 3.90. Found: C, 83.81; H, 8.04; N, 3.73.

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Supporting Information Available: Analytical data for all starting materials and products not listed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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