Synthesis of 3-Aryl-3-hydroxypyrrolidin-2-ones and 2-Benzyl-9*b*-hydroxy-3,3*a*,5,9*b*-tetrahydro-2*H*-pyrrolo[3,4-*c*]quinoline-1,4-dione Derivatives from the Baylis-Hillman Adducts of Isatins

Seung Chan Kim, Ka Young Lee, Saravanan Gowrisankar, and Jae Nyoung Kim*

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea
**E-mail: kimjn@chonnam.ac.kr*
Received March 20, 2006

We prepared 3-aryl-3-hydroxypyrrolidin-2-one and tricyclic 2-benzyl-9*b*-hydroxy-3,3*a*,5,9*b*-tetrahydro-2*H*-pyrrolo[3,4-*c*]quinoline-1,4-dione derivatives starting from the Baylis-Hillman adducts of isatin derivatives.

Key Words : 3-Aryl-3-hydroxypyrrolidin-2-ones, Pyrrolo[3,4-*c*]quinolinones, Baylis-Hillman adducts, Isatins

Introduction

Recently, synthesis of 3,4-disubstituted pyrrolidin-2-one derivatives has been investigated extensively[1,2] in connection with the design of conformationally restricted analogs of bioactive amino acids[2] and with the usefulness as intermediates in the synthesis of bioactive nonproteinogenic amino acids.[2f] Especially, the synthesis of 3-hydroxypyrrolidin-2-one derivatives received much attention,[1h,1i,3,4a-c] which involved the trials of oxidation of chiral pyrrolidin-2-one[3] or synthesis from the Baylis-Hillman adduct of α-keto esters.[4a-c] A new tryptamine-related alkaloid, chimonamidine (**1**, Figure 1), was isolated from the seeds of *Chimonanthus praecox Link* and the absolute stereochemistry was elucidated by spectroscopic analysis and biomimetic total synthesis from tryptamine.[3] The structure of donaxaridine (**2**), an alkaloid isolated from *Arundo donax*, was initially suggested to be the one in the parenthesis.[5b-d] However, it has been modified recently to have the same backbone with that of chimonamidine.[5a] Inoue and Hirama have used 3-aryl-3-hydroxypyrrolidin-2-one derivative **3** in their synthesis of potent proteasome inhibitors TMC-95A (Figure 1).[5e]

Results and Discussion

In these contexts of the importance of 3,4-disubstituted 3-hydroxypyrrolidin-2-ones,[1-5] especially the compounds having 2-aminophenyl group at the 3-position,[3,5] we started to develop an efficient synthetic method for these valuable compounds. At the early stage of this study, we examined the synthetic strategy shown in Scheme 1. Baylis-Hillman reaction of acrylonitrile and methyl phenylglyoxylate afforded the corresponding Baylis-Hillman adduct **4** as reported.[4a,4e,4f] The reaction of benzylamine and **4** gave the desired 3-hydroxy-4-cyanopyrolidin-2-one derivative **5** in 86% yield as a diastereomeric mixture *via* the successive Michael addition and intramolecular condensation reaction.[4]

As the groups of Amri and Orena have examined such synthetic strategy in detail,[2,4] we estimated the method would be the best choice for the synthesis of 3-hydroxypyrrolidin-2-ones. However, we needed phenylglyoxylate derivative having an amino group at the *ortho*-position in order reach the basic skeleton of chimonamidine or donaxaridine (Figure 1). However, we could not find any reasonable method either for the synthesis of 2-aminophenylglyoxylate

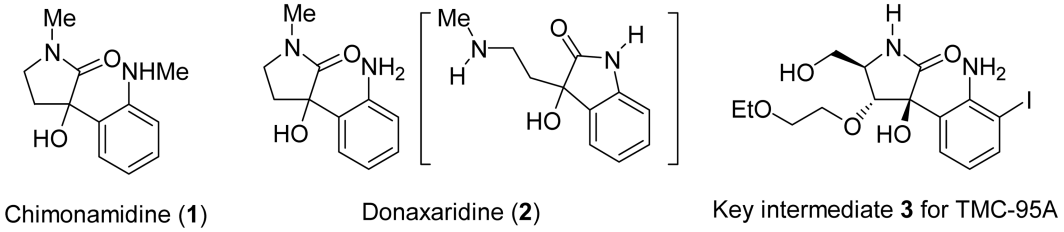
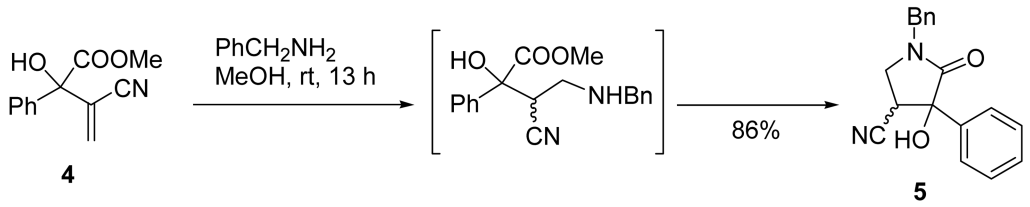
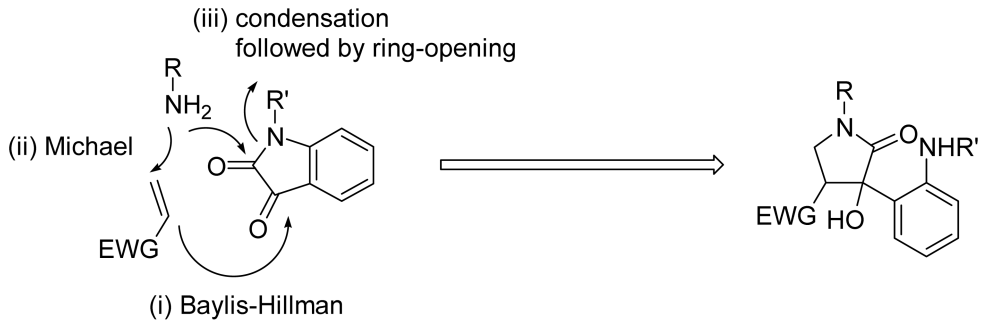


Figure 1

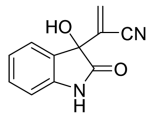
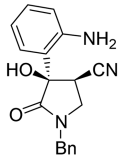
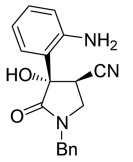
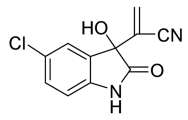
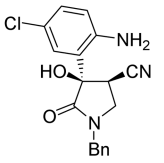
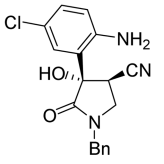
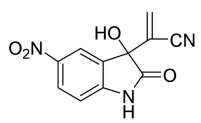
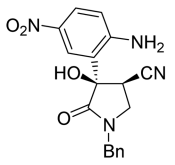
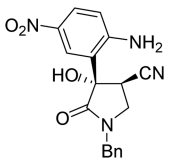


Scheme 1



Scheme 2

Table 1. The reaction of Baylis-Hillman adducts of acrylonitrile and benzylamine[a]

Entry	Substrate	Time (h)	Product (%)	
1	 **6a**	20	 **7a**-*syn* (57)	 **7a**-*anti* (31)
2	 **6b**	10	 **7b**-*syn* (49)	 **7b**-*anti* (18)
3	 **6c**	2	 **7c**-*syn* (57)	 **7c**-*anti* (19)

[a]Conditions: $BnNH_2$ (1.2 equiv), MeOH, rt.

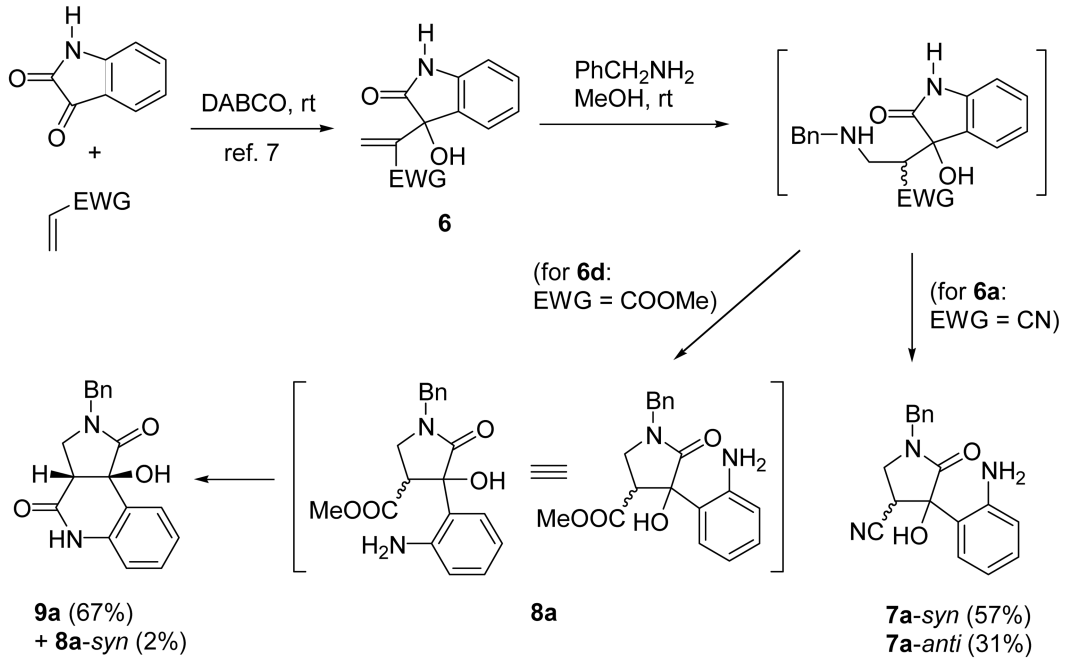
derivatives or for the introduction of amino group (or its protected form) at the *ortho*-position of the aryl group of **5**.

Thus, we thought another synthetic route for the preparation of *ortho*-aminoaryl-substituted pyrrolidinone derivatives, which have similar backbone with those of the natural products, chimonamidine and donaxaridine. With the experiences on the chemical transformations of the Baylis-Hillman adducts,[6,7] we envisioned that we could prepare the interesting 3,4-disubstituted 3-aryl-3-hydroxypyrolidin-2-one derivatives as in Scheme 2. If we used the Baylis-Hillman adducts of isatin,[7] we could synthesize our desired compound easily *via* the Michael addition, condensation, and the following ring-opening sequences.

The synthesis of the Baylis-Hillman adducts of isatin **6a-f** has been already published by us and other group independently (Scheme 3).[7] With the Baylis-Hillman adduct **6a** in our hand, we examined the reaction of **6a** and benzylamine.[2,8] As expected, the reaction of benzylamine and **6a** in MeOH at room temperature gave a diastereomeric mixture of **7a**-*syn* and **7a**-*anti* in 57 and 31% yield, respectively (Scheme 3 and entry 1 in Table 1).[9] Similarly, we could obtain **7b** and **7c** and the results are summarized in Table 1. In all cases, the *syn* isomers were obtained as the major products. The stereochemistry of **7b**-syn was confirmed by NOE experiments as shown in Figure 2.

However, the situation was different for the Baylis-Hillman adducts derived from methyl acrylate (Scheme 3 and Table 2). Indeed, when the Baylis-Hillman adduct **6d** was used as the starting material, low yield (2%) of the expected 3-hydroxypyrrolidin-2-one derivative **8a**-*syn* was obtained together with tricyclic 2-benzyl-9b-hydroxy-3,3a,5,9b-tetrahydro-2*H*-pyrrolo[3,4-*c*]quinolone-1,4-dione **9a** (67%) as a major product (entry 1 in Table 2).[9] The compound **9a** was formed in a one-pot reaction *via* the sequential Michael addition of benzylamine to the Baylis-Hillman adduct **6d**, intramolecular cyclization and concomitant ring opening of lactam of isatin moiety,[5b-d] and eventual formation of new lactam ring (Scheme 3). Similarly, we obtained **9b** from the reaction of **6d** and *p*-methoxybenzylamine and **9c** from **6e** and benzylamine. The stereochemistry of compounds **9** was confirmed by NOE experiments with **9c**, as an example (Figure 2). But, the situation was different for **6f**, which afforded a diastereomeric mixture of **8d**. However, the relative *syn/anti* ratio was inverted with respect to **6a-c**. In this case we could not find the formation of the corresponding tricyclic compound **9d**. The cyclization was difficult for **8d** between the ester and –NHBn moiety. The whole results are summarized in Table 2.

For the next trial, we examined the synthesis of 2,3-dihydropyrrolo[3,4-*c*]quinoline skeleton from **7-9** by treatment with *p*-TsOH in benzene.[10] As shown in entry 1 (Table 3), 2,3-dihydropyrrolo[3,4-*c*]quinoline derivative **10a** was obtained in 88% yield by dehydration of **9b**. The compound **10a** was obtained directly from **8b**-*syn* under the same conditions, although the yields were moderate (entry 2). In this case, unusual tricyclic compound **11a** was obtained together with **10a** *via* the mechanism as proposed in Scheme 4.[11] As shown, **10a** might be formed by the successive cyclization and dehydration (pathway-a) from **8b**-*syn*. When the reaction occurred along the pathway-b, tricyclic compound **11a** could be generated. From the reaction of **7a**-*syn* or **7a**-*anti* we obtained **10b** in moderate yields (entries 3 and 4) together with recovered starting materials. But, the



Scheme 3

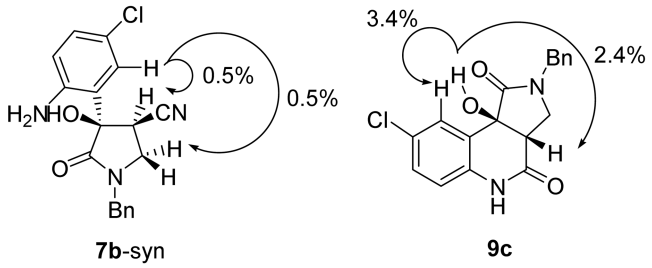


Figure 2

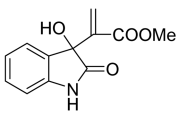
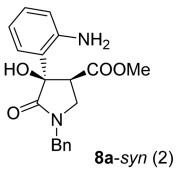
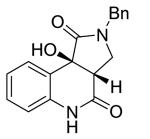
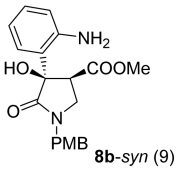
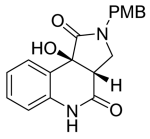
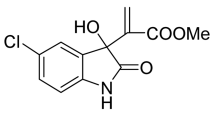
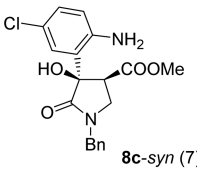
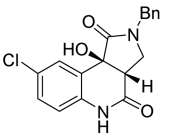
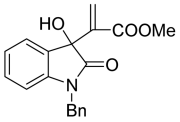
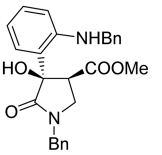
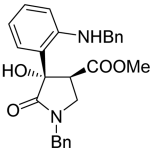
reaction of **8d**-*anti* under the same reaction conditions showed no reaction.

In summary, we disclosed the synthesis of 3-ary-3-hydroxypyrrolidin-2-ones and tricyclic 2-benzyl-9b-hydroxy-3,3a,5,9b-tetrahydro-2*H*-pyrrolo[3,4-*c*]quinoline-1,4-diones starting from the Baylis-Hillman adducts of isatin derivatives. The biological activities of synthesized compounds will be evaluated in their present form and as their hydrolyzed form.

Experimental Section

General procedure. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ or in $CDCl_3$ + DMSO-d_6. The signal positions are reported in ppm relative to TMS (δ scale) used as an internal standard. IR spectra are reported in cm^{-1}. Mass spectra were obtained from the Korea Basic Science Institute (Gwangju branch). Melting points are uncorrected. The elemental analyses were carried out at Korea Research Institute of Chemical Technology, Taejon, Korea. All reagents were purchased from commercial sources and used without further treatment. The separations were carried out by flash column chromatography over silica gel (230-400 mesh ASTM). Organic extracts were dried over anhydrous $MgSO_4$ and the solvents were evaporated on a rotary evaporator under water aspirator pressure.

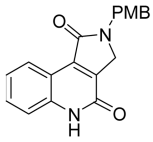
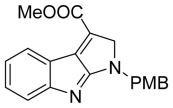
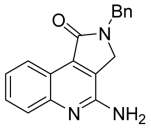
Table 2. The reaction of Baylis-Hillman adducts of methyl acrylate and benzylamine[a]

Entry	Substrate	Time (h)	Product (%)	
1	 **6d**	4	 **8a**-*syn* (2)	 **9a** (67)
2[b]	**6d**	2	 **8b**-*syn* (9)	 **9b** (69)
3	 **6e**	2	 **8c**-*syn* (7)	 **9c** (68)
4	 **6f**	20	 **8d**-*syn* (8)	 **8d**-*anti* (76)

[a]Conditions: $BnNH_2$ (1.2 equiv), MeOH, rt. [b]4-Methoxybenzylamine was used instead of benzylamine (PMB is 4-methoxybenzyl).

Synthesis of Baylis-Hillman adduct 4 and 3-hydroxy-

Table 3. Synthesis of 2,3-dihydropyrrolo[3,4]c]quinoline derivatives

Entry	Substrate	Time (h)	Product (%)
1	**9b**	*p*-TsOH (0.2 equiv) benzene, reflux, 80 h	 **10a** (88)
2	**8b**-*syn*	*p*-TsOH (0.2 equiv) benzene, reflux, 17 h	**10a** (24%)  **11a** (32)
3	**7a**-*syn*	*p*-TsOH (0.5 equiv) toluene, reflux, 15 h	 **10b** (43) recovered **7a**-*syn* (51)
4	**7a**-*anti*	*p*-TsOH (0.5 equiv) toluene, reflux, 22 h	**10b** (54) + recovered **7a**-*anti* (43)
5	**8d**-*anti*	*p*-TsOH (0.5 equiv) benzene, reflux, 36 h	no reaction

pyrrolidin-2-one 5. The Baylis-Hillman adduct **4** was synthesized according to the reported method.[4] The reaction of **4** and benzylamine in MeOH at room temperature gave **5** in 86% yield as a diastereomeric mixture after column chromatographic purification process. The analytical samples of each isomer were obtained by flash column chromatography (hexanes/EA, 3 : 2), but we did not determine the stereochemistry.

Compound 4: 65% yield; white solid, mp 78-80 °C; IR (KBr) 3521, 2233, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ3.95 (s, 3H), 4.13 (s, 1H), 6.15 (s, 1H), 6.20 (s, 1H), 7.37-7.44 (m, 3H), 7.48-7.53 (m, 2H).

Major isomer of compound 5: IR (film) 3417, 2252, 1689, 1647 cm^{-1}; ^1H NMR ($CDCl_3$ + three drops of DMSO-d_6, 300 MHz) δ3.31 (t, J = 7.5 Hz, 1H), 3.48 (dd, J = 9.6 and 7.5 Hz, 1H), 3.66 (dd, J = 9.6 and 7.5 Hz, 1H), 4.56 (d, J = 14.7 Hz, 1H), 4.65 (d, J = 14.7 Hz, 1H), 6.58 (s, 1H), 7.29-7.43 (m, 8H), 7.49-7.52 (m, 2H); ^{13}C NMR ($CDCl_3$ + three drops of DMSO-d_6, 75 MHz), δ39.09, 45.44, 46.79, 77.81, 115.98, 125.65, 127.80 (2C), 128.27, 128.34, 128.70, 134.83, 139.37, 171.66; ESIMS *m/z* 293 (M^++H). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.87; H, 5.61; N, 9.54.

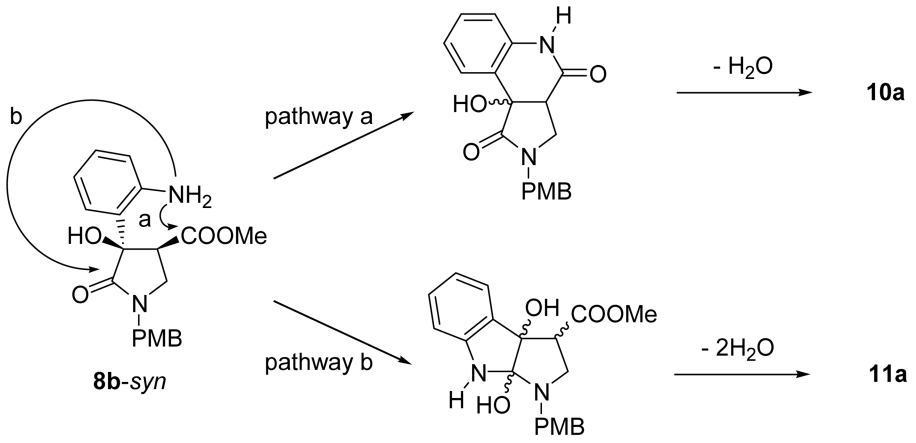
Minor isomer of compound 5: IR (film) 3420, 2249, 1705, 1026 cm^{-1}; ^1H NMR ($CDCl_3$ + three drops of DMSO-d_6, 300 MHz) δ3.32 (t, J = 7.5 Hz, 1H), 3.55-3.67 (m, 2H), 4.61 (d, J = 14.7 Hz, 1H), 4.67 (d, J = 14.7 Hz, 1H), 6.24 (br s, 1H), 7.32-7.45 (m, 10H); ^{13}C NMR ($CDCl_3$ + three drops of DMSO-d_6, 75 MHz) δ38.51, 44.83, 46.97, 79.51, 116.51, 125.60, 128.05, 128,16, 128.30, 128.68, 128.80, 134.66, 137.58, 172.34.

Synthesis of the Baylis-Hillman adducts of isatin. The Baylis-Hillman adducts of isatins **6a-f** were synthesized according to the previous method[7] and the spectroscopic data of **6b**, **6c**, and **6e** are as follows. The other compounds **6a**, **6d** and **6f** were already known.[7a]

Compound 6b: 56%; white solid, mp 175-177 °C (dec.); IR (KBr) 3398, 2233, 1743 cm^{-1}; ^1H NMR ($CDCl_3$ + three drops of DMSO-d_6, 300 MHz) δ6.18 (s, 1H), 6.39 (s, 1H), 6.81 (br s, 1H), 6.88 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.29 (s, 1H), 10.23 (br s, 1H); ^{13}C NMR ($CDCl_3$ + three drops of DMSO-d_6, 75 MHz) δ 76.27, 111.53, 115.58, 122.65, 124.69, 127.45, 129.95, 130.14, 131.23, 140.15, 175.24.

Compound 6c: 47%; white solid, mp 143-145 °C; IR (KBr) 2229, 1720, 1527, 1342 cm^{-1}; ^1H NMR ($CDCl_3$ + three drops of DMSO-d_6, 300 MHz) δ6.26 (s, 1H), 6.49 (s, 1H), 7.05 (d, J = 8.7 Hz, 1H), 7.10 (s, 1H), 8.21 (s, 1H), 8.24 (d, J = 8.7 Hz, 1H), 10.92 (br s, 1H); ^{13}C NMR ($CDCl_3$ + three drops of DMSO-d_6, 75 MHz) δ75.96, 110.36, 115.38, 120.53, 122.05, 126.98, 129.47, 131.88, 143.03, 147.96, 175.63.

Compound 6e: 81%; yellow solid, mp 202-204 °C (dec.); IR (KBr) 3259, 1721, 1701 cm^{-1}; ^1H NMR ($CDCl_3$ + three drops of DMSO-d_6, 300 MHz) δ3.62 (s, 3H), 6.15 (br s, 1H), 6.58 (s, 1H), 6.61 (s, 1H), 6.84 (d, J = 8.1 Hz, 1H), 7.06 (d, J = 2.1 Hz, 1H), 7.18 (dd, J = 8.1 and 2.1 Hz, 1H), 9.87 (br s, 1H); ^{13}C NMR ($CDCl_3$ + three drops of DMSO-d_6, 75



Scheme 4

MHz) δ 51.34, 75.48, 110.78, 123.66, 126.39, 127.69, 128.88, 132.63, 138.58, 141.11, 164.49, 177.36.

Synthesis of 3-aryl-3-hydroxypyrrolidin-2-one derivatives 7a-c. Typical experimental procedure for the reaction of **6a** and benzylamine: A mixture of **6a** (200 mg, 1.0 mmol) and benzylamine (129 mg, 1.2 mmol) in MeOH (4 mL) was stirred at room temperature for 20 h. After removal of solvent and column chromatographic purification process (hexanes/EA, 3 : 2) we obtained **7a**-*syn* (175 mg, 57%) and **7a**-*anti* (96 mg, 31%).[9] Other compounds were synthesized similarly and the spectroscopic data of **7b** and **7c** are as follows.

Compound 7b-*syn*: 49%; yellow solid, mp 166-168 °C; IR (KBr) 3433, 3344, 3255, 2249, 1693, 1612 cm^{-1}; ^1H NMR ($CDCl_3$ + three drops of DMSO-d_6, 300 MHz) δ 3.26 (dd, J = 10.5 and 6.6 Hz, 1H), 3.48 (dd, J = 10.5 and 2.7 Hz, 1H), 3.84 (dd, J = 6.6 and 2.7 Hz, 1H), 4.59 (d, J = 14.4 Hz, 1H), 4.62 (br s, 2H), 4.69 (d, J = 14.4 Hz, 1H), 6.67 (d, J = 8.7 Hz, 1H), 6.76 (br s, 1H), 6.88 (d, J = 2.4 Hz, 1H), 7.06 (dd, J = 8.7 and 2.4 Hz, 1H), 7.28-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$ + three drops of DMSO-d_6, 75 MHz) δ 35.24, 45.64, 46.94, 78.52, 117.23, 118.81, 122.19, 123.49, 126.12, 127.93 (2C), 128.78, 129.30, 134.38, 144.33, 171.15; ESIMS *m/z* 342 (M^++H). Anal. Calcd for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29. Found: C, 63.19; H, 4.87; N, 12.21.

Compound 7b-*anti*: 18%; yellow solid, mp 167-168 °C; IR (KBr) 3494, 3383, 3248, 2252, 1689, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, three drops of DMSO-d_6, 300 MHz) δ 3.31 (dd, J = 9.9 and 6.0 Hz, 1H), 3.66 (dd, J = 9.9 and 7.8 Hz, 1H), 3.76 (dd, J = 7.8 and 6.0 Hz, 1H), 4.55 (d, J = 14.7 Hz, 1H), 4.70 (d, J = 14.7 Hz, 1H), 4.91 (br s, 2H), 6.66 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 2.7 Hz, 1H), 7.06 (dd, J = 8.4 and 2.7 Hz, 1H), 7.13 (br s, 1H), 7.32-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.25, 45.35, 46.71, 80.34, 116.84, 118.32, 121.01, 122.17, 126.61, 127.79 (2C), 128.67, 129.15, 134.37, 145.76, 171.03; ESIMS *m/z* 342 (M^++H). Anal. Calcd for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29. Found: C, 63.11; H, 4.92; N, 12.25.

Compound 7c-*syn*: 57%; yellow solid, mp 204-205 °C (dec.); IR (KBr) 3460, 3371, 3344, 2249, 1678, 1624, 1577, 1489 cm^{-1}; ^1H NMR ($CDCl_3$ + three drops of DMSO-d_6, 300 MHz) δ 3.26 (dd, J = 10.5 and 6.6 Hz, 1H), 3.51 (dd, J = 10.5 and 3.0 Hz, 1H), 3.65 (dd, J = 6.6 and 3.0 Hz, 1H), 4.57 (d, J = 14.7 Hz, 1H), 4.82 (d, J = 14.7 Hz, 1H), 5.82 (br s, 2H), 6.72 (d, J = 9.0 Hz, 1H), 7.25 (br s, 1H), 7.29-7.43 (m, 5H), 7.80 (d, J = 2.7 Hz, 1H), 7.98 (dd, J = 9.0 and 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$ + three drops of DMSO-d_6, 75 MHz) δ 35.87, 45.72, 47.23, 78.85, 116.08, 117.02, 120.23, 123.25, 125.96, 128.10, 128.13, 128.97, 134.22, 137.46, 152.74, 170.57; ESIMS *m/z* 353 (M^++H). Anal. Calcd for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.33; H, 4.67; N, 15.76.

Compound 7c-*anti*: 19%; yellow solid, mp 188-190 °C (dec); IR (KBr) 3629, 3487, 3359, 2252, 1678, 1620, 1581, 1493 cm^{-1}; ^1H NMR ($CDCl_3$, three drops of DMSO-d_6, 300 MHz) δ 3.29 (dd, J = 9.6 and 6.3 Hz, 1H), 3.66 (dd, J = 9.6 and 8.1 Hz, 1H), 3.74 (dd, J = 8.1 and 6.3 Hz, 1H), 4.55 (d, J = 14.7 Hz, 1H), 4.82 (d, J = 14.7 Hz, 1H), 6.16 (br s, 2H), 6.73 (d, J = 9.3 Hz, 1H), 7.32-7.45 (m, 6H), 7.87 (d, J = 2.7 Hz, 1H), 8.00 (dd, J = 9.3 and 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.58, 45.12, 46.94, 80.78, 115.68, 116.49, 117.68, 123.87, 125.84, 127.89, 127.92, 128.80, 134.11, 136.63, 153.78, 170.58; ESIMS *m/z* 353 (M^++H). Anal. Calcd for $C_{18}H_{16}N_4O_4$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.27; H, 4.54; N, 15.72.

Synthesis of tetrahydro-2*H*-pyrrolo[3,4-*c*]quinoline derivatives. Typical experimental procedure for the reaction of **6d** and benzylamine: A mixture of **6d** (233 mg, 1.0 mmol) and benzylamine (129 mg, 1.2 mmol) in MeOH (4 mL) was stirred at room temperature for 4 h. After removal of solvent and column chromatographic purification process (hexanes/EA, 3 : 2) we obtained **8a**-*syn* (7 mg, 2%) and **9a** (207 mg, 67%).[9] Other compounds were synthesized similarly and the spectroscopic data of **8b-d**, **9b**, and **9c** are as follows.

Compound 8b-*syn*: 9%; IR (film) 3641, 3483, 3371, 3221, 2958, 1736, 1693, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.14 (dd, J = 10.5 and 6.3 Hz, 1H), 3.42 (d, J = 10.5 Hz, 1H), 3.71 (s, 3H), 3.71-3.83 (m, 1H), 3.80 (s, 3H), 4.12 (br s, 1H), 4.56 (br s, 2H), 4.59 (s, 2H), 6.63 (t, J = 7.5 Hz, 1H), 6.70 (d, J = 7.5 Hz, 1H), 6.83 (dd, J = 7.8 and 1.5 Hz, 1H), 6.89 (d, J = 8.7 Hz, 2H), 7.10 (t, J = 7.8 Hz, 1H), 7.27 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.31, 46.81, 47.42, 52.14, 55.26, 80.44, 114.07, 117.66, 117.76, 123.51, 125.94, 127.06, 129.61, 129.89, 145.80, 159.32, 171.01, 172.56; ESIMS *m/z* 371 (M^++H). Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.91; H, 6.05; N, 7.48.

Compound 9b: 69%; white solid, mp 206-207 °C; IR (KBr) 3394, 3205, 3070, 1697, 1666, 1242 cm^{-1}; ^1H NMR ($CDCl_3$ + three drops of DMSO-d_6, 300 MHz) δ 3.10 (t, J = 8.7 Hz, 1H), 3.33 (t, J = 8.7 Hz, 1H), 3.57 (t, J = 8.7 Hz, 1H), 3.76 (s, 3H), 4.32 (d, J = 14.7 Hz, 1H), 4.49 (d, J = 14.7 Hz, 1H), 5.28 (br s, 1H), 6.77-6.92 (m, 3H), 7.04-7.11 (m, 3H), 7.24-7.33 (m, 1H), 7.87 (dd, J = 7.8 and 1.2 Hz, 1H), 9.78 (s, 1H); ^{13}C NMR ($CDCl_3$ + three drops of DMSO-d_6, 75 MHz) δ 44.83, 46.13, 47.16, 54.96, 74.57, 113.83, 115.60, 119.84, 123.27, 127.07, 127.84, 128.97, 129.76, 136.08, 158.87, 167.84, 172.44; ESIMS *m/z* 339 (M^++H). Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.25; H, 5.41; N, 8.19.

Compound 8c-*syn*: 7%; IR (film) 3371, 2958, 1736, 1689 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.09 (dd, J = 10.2 and 6.3 Hz, 1H), 3.38 (d, J = 10.2 Hz, 1H), 3.58 (d, J = 6.3 Hz, 1H), 3.64 (s, 3H), 4.47 (br s, 3H), 4.49 (d, J = 14.4 Hz, 1H), 4.67 (d, J = 14.4 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.72 (s, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.20-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.46, 47.32, 47.58, 52.25, 80.00, 118.63, 122.40, 124.74, 125.91, 128.08, 128.58, 128.87, 129.38, 134.88, 144.38, 170.68, 172.14; ESIMS *m/z* 375 (M^++H). Anal. Calcd for $C_{19}H_{19}ClN_2O_4$: C, 60.88; H, 5.11; N, 7.47. Found: C, 60.80; H, 5.19; N, 7.41.

Compound 9c: 68%; white solid, mp 215-217 °C (dec.); IR (KBr) 3402, 3190, 3066, 1693, 1662, 1489, 1408 cm^{-1}; ^1H NMR ($CDCl_3$ + three drops of DMSO-d_6, 300 MHz) δ

3.15-3.29 (m, 2H), 3.60 (dd, J = 9.3 and 7.8 Hz, 1H), 4.37 (d, J = 15.0 Hz, 1H), 4.51 (d, J = 15.0 Hz, 1H), 6.57 (br s, 1H), 6.94 (d, J = 8.4 Hz, 1H), 7.14-7.16 (m, 2H), 7.20-7.32 (m, 4H), 7.77 (d, J = 2.1 Hz, 1H), 10.55 (s, 1H); ^{13}C NMR ($CDCl_3$ + three drops of DMSO-d_6, 75 MHz) δ 43.82, 44.98, 45.39, 72.84, 115.52, 120.99, 125.54, 126.03, 126.06, 126.52, 127.08, 127.88, 133.82, 134.12, 166.14, 170.47; ESIMS *m/z* 343 (M^++H). Anal. Calcd for $C_{18}H_{15}ClN_2O_3$: C, 63.07; H, 4.41; N, 8.17. Found: C, 63.14; H, 4.59; N, 8.05.

Compound 8d-*syn*: 8%; IR (film) 3390, 3298, 1743, 1689, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.25-3.44 (m, 3H), 3.37 (s, 3H), 3.79 (d, J = 12.9 Hz, 1H), 3.94 (d, J = 12.9 Hz, 1H), 4.77 (d, J = 15.9 Hz, 1H), 4.93 (d, J = 15.9 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 6.96 (t, J = 7.8 Hz, 1H), 7.14-7.20 (m, 2H), 7.22-7.37 (m, 11H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.96, 46.42, 48.30, 51.79, 53.69, 77.27, 109.29, 122.77, 124.28, 127.47, 127.53, 127.61, 128.39, 128.62, 128.72, 129.24, 129.65, 135.66, 138.42, 142.81, 170.90, 176.90; ESIMS *m/z* 431 (M^++H). Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.33; H, 6.19; N, 6.44.

Compound 8d-*anti*: 76%; white solid, mp 53-55 °C; IR (film) 3545, 3429, 3305, 1724, 1616, 1362 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.09 (dd, J = 12.6 and 4.5 Hz, 1H), 3.30 (s, 3H), 3.38 (dd, J = 11.4 and 4.5 Hz, 1H), 3.89-4.04 (m, 3H), 4.80 (d, J = 15.6 Hz, 1H), 4.97 (d, J = 15.6 Hz, 1H), 6.64 (d, J = 7.8 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.21-7.39 (m, 11H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.83, 46.53, 50.72, 51.77, 53.54, 76.36, 109.14, 122.77, 123.95, 127.41, 127.47 (2C), 128.28, 128.62, 128.66, 129.19, 129.74, 135.79, 138.59, 142.93, 170.57, 176.98; ESIMS *m/z* 431 (M^++H). Anal. Calcd for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.41; H, 6.11; N, 6.37.

Synthesis of dihydropyrrolo[3,4-*c*]quinoline derivatives. Typical procedure for the synthesis of **10a**: A mixture of **9b** (169 mg, 0.5 mmol) and *p*-toluenesulfonic acid monohydrate (19 mg, 0.1 mmol) in benzene (5 mL) was heated to reflux for 80 h. After usual aqueous work-up and column chromatographic purification process (hexanes/EA, 3 : 2) we obtained **10a** as a white solid, 141 mg (88%). Other experiments were carried out similarly and the spectroscopic data of **10a**, **10b**, and **11a** are as follows.

Compound 10a: 88%; white solid, mp 231-233 °C; IR (KBr) 1670, 1574, 1439 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.80 (s, 3H), 4.29 (s, 2H), 4.77 (s, 2H), 6.88 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.32-7.41 (m, 2H), 7.56 (t, J = 7.8 Hz, 1H), 8.87 (d, J = 8.1 Hz, 1H), 11.51 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.03, 47.78, 55.31, 114.33, 115.83, 116.14, 123.59, 124.67, 128.54, 129.73, 130.97, 134.97, 139.02, 139.11, 159.38, 160.04, 167.42; ESIMS *m/z* 321 (M^++H). Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.32; H, 5.27; N, 8.59.

Compound 10b: 54% (from **7a**-*anti*); white solid, mp 90-92 °C; IR (KBr) 3429, 3332, 3136, 1724, 1689, 1662, 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.15 (s, 2H), 4.83 (s, 2H), 4.93 (br s, 2H), 7.25-7.39 (m, 5H), 7.43 (t, J = 7.8 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 8.92 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.42, 46.99, 119.82, 123.57, 124.18, 124.89, 125.89, 127.92, 128.15, 128.93, 130.10, 136.43, 136.59, 147.81, 151.69, 168.12; ESIMS *m/z* 290 (M^++H). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.69; H, 5.31; N, 14.45.

Compound 11a: 32%; white solid, mp 170-172 °C; IR (film) 2962, 1682, 1512, 1257 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.79 (s, 3H), 4.11 (s, 3H), 4.27 (s, 2H), 4.79 (s, 2H), 6.87 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.53 (t, J = 7.8 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 8.97 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.90, 47.04, 53.53, 55.30, 114.27, 121.09, 123.70, 125.30, 127.02, 127.20, 128.89, 129.64, 129.80, 137.85, 147.12, 157.32, 159.29, 167.84; ESIMS *m/z* 335 (M^++H). Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.67; H, 5.49; N, 8.31.

Acknowledgments. This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD) (KRF-2005-041-C00248). Spectroscopic data was obtained from the Korea Basic Science Institute, Gwangju branch.

References and Notes

1. For the synthesis and biological activities of pyrrolidinone derivatives, see: (a) Choi, M. K.-W.; Yu, W.-Y.; Che, C.-M. *Org. Lett.* **2005**, *7*, 1081. (b) Yee, N. K.; Dong, Y.; Kapadia, S. R.; Song, J. J. *J. Org. Chem.* **2002**, *67*, 8688. (c) Kagoshima, H.; Okamura, T.; Akiyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 7182. (d) Singh, V.; Saxena, R.; Batra, S. *J. Org. Chem.* **2005**, *70*, 353. (e) Gagosz, F.; Moutrille, C.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 2707. (f) Elworthy, T. R.; Brill, E. R.; Chiou, S.-S.; Chu, F.; Harris, J. R.; Hendricks, R. T.; Huang, J.; Kim, W.; Lach, L. K.; Mirzadegan, T.; Yee, C.; Walker, K. A. M. *J. Med. Chem.* **2004**, *47*, 6124. (g) Bower, J. F.; Svenda, J.; Williams, A. J.; Charmant, J. P. H.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Lett.* **2004**, *6*, 4727. (h) Puschl, A.; Boesen, T.; Zuccarello, G.; Dahl, O.; Pitsch, S.; Nielsen, P. E. *J. Org. Chem.* **2001**, *66*, 707. (i) Brabandt, W. V.; De Kimpe, N. *J. Org. Chem.* **2005**, *70*, 3369. (j) Serna, S.; Tellitu, I.; Dominguez, E.; Moreno, I.; SanMartin, R. *Org. Lett.* **2005**, *7*, 3073. (k) Othman, R. B.; Bousquet, T.; Fousse, A.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 2825. (l) Taylor, E. C.; Liu, B. *J. Org. Chem.* **2001**, *66*, 3726. (m) Cossy, J.; Madaci, A.; Pete, J.-P. *Tetrahedron Lett.* **1994**, *35*, 1541. (n) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592. (o) Blay, G.; Fernandez, I.; Monje, B.; Pedro, J. R. *Tetrahedron* **2004**, *60*, 165.
2. (a) Galeazzi, R.; Geremia, S.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1996**, *7*, 3573. (b) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1999**, *55*, 4029. (c) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1999**, *55*, 261. (d) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1997**, *8*, 133. (e) Fava, C.; Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **2003**, *14*, 3697. (f) Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Rinaldi, S. *Tetrahedron: Asymmetry* **2003**, *14*, 3353. (g) Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1996**, *52*, 1069. (h) Galeazzi, R.; Geremia, S.; Mobbili, G.; Orena, M. *Tetrahedron: Asymmetry* **1996**, *7*, 79.
3. Synthesis of natural chimonamidine, Takayama, H.; Matsuda, Y.; Masubuchi, K.; Ishida, A.; Kitajima, M.; Aimi, N. *Tetrahedron* **2004**, *60*, 893.

4. For the synthesis of Baylis-Hillman adducts of β-ketoesters and synthesis of pyrrolidinone derivatives, see: (a) Amri, H.; El Gaied, M. M.; Ben Ayed, T.; Villieras, J. *Tetrahedron Lett.* **1992**, *33*, 7345. (b) Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Rinaldi, S. *Tetrahedron: Asymmetry* **2004**, *15*, 3249. (c) Ben Ayed, T.; Amri, H.; El Gaied, M. M.; Villieras, J. *Tetrahedron* **1995**, *51*, 9633. (d) Beltaief, I.; Besbes, R.; Ben Amor, F.; Amri, H.; Villieras, M.; Villieras, J. *Tetrahedron* **1999**, *55*, 3949. (e) Basavaiah, D.; Sreenivasulu, B.; Rao, A. L. *J. Org. Chem.* **2003**, *68*, 5983. (f) Basavaiah, D.; Bharati, T. K.; Gowriswari, V. V. L. *Tetrahedron Lett.* **1987**, *28*, 4351.
5. (a) Khuzhaev, V. U. *Chemistry of Natural Compounds* **2004**, *40*, 516. (b) Khuzhaev, V. U.; Tashkhodzhaev, B.; Aripova, S. F. *Khim. Prir. Soedin*. **1995**, 720. (c) Rasmussen, H. B.; MacLeod, J. K. *J. Nat. Prod*. **1997**, *60*, 1152. (d) Kawasaki, T.; Nagaoka, M.; Satoh, T.; Okamoto, A.; Ukon, R.; Ogawa, A. *Tetrahedron* **2004**, *60*, 3493. (e) Inoue, M.; Sakazaki, H.; Furuyama, H.; Hirama, M. *Angew. Chem. Int. Ed*. **2003**, *42*, 2654.
6. For leading references of our papers, see: (a) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481. (b) Lee, K. Y.; Lee, C. G.; Na, J. E.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 69. (c) Lee, C. G.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron* **2005**, *61*, 1493. (d) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 4859. (e) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 5387. (f) Park, D. Y.; Lee, M. J.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 8799. (g) Lee, K. Y.; Kim, S. C.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 977. (h) Lee, M. J.; Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 1355 and further references cited therein.
7. For the synthesis of Baylis-Hillman adducts of isatin derivatives, see: (a) Chung, Y. M.; Im, Y. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 1651. (b) Garden, S. J.; Skakle, J. M. S. *Tetrahedron Lett.* **2002**, *43*, 1969.
8. Addition of benzylamine to B-H adducts, Perlmutter, P.; Tabone, M. *Tetrahedron Lett.* **1988**, *29*, 949.
9. The preliminary result of this paper was reported in *Tetrahedron Lett.* **2006**, *47*, 3463.
10. For the synthesis and biological activity of pyrrolo[3,4-*c*]quinolinone derivatives, see: (a) Kravchenko, D. V.; Kuzovkova, Y. A.; Kysil, V. M.; Tkachenko, S. E.; Maliarchouk, S.; Okun, I. M.; Balakin, K. V.; Ivachtchenko, A. V. *J. Med. Chem.* **2005**, *48*, 3680. (b) Cappelli, A.; Anzini, M.; Vomero, S.; Mennuni, L.; Makovec, F.; Doucet, E.; Hamon, M.; Menziani, M. C.; De Benedetti, P. G.; Giorgi, G.; Ghelardini, C.; Collina, S. *Bioorg. Med. Chem.* **2002**, *10*, 779.
11. For the synthesis of similar 1,2-dihydropyrrolo[2,3-*b*]indole derivatives, see: (a) Molina, P.; Arques, A.; Alias, A.; Vinader, M. V. *Tetrahedron Lett.* **1991**, *32*, 4401. (b) Bailey, P. D.; Cochrane, P. J.; Irvine, F.; Morgan, K. M.; Pearson, D. P. J.; Veal, K. T. *Tetrahedron Lett.* **1999**, *40*, 4593. (c) Molina, P.; Arques, A.; Alias, A.; Vinader, M. V. *Tetrahedron* **1992**, *48*, 3091.