Tetrahedron Letters 52 (2011) 6122–6126

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

One-pot synthesis of pyrrolidino- and piperidinoquinolinones by three-component aza-Diels–Alder reactions of in situ generated *N*-arylimines and cyclic enamides

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ARTICLE INFO

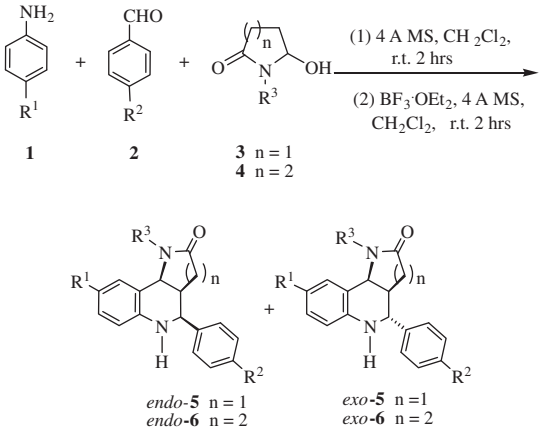
Article history:
Received 10 July 2011
Revised 29 August 2011
Accepted 6 September 2011
Available online 10 September 2011

Keywords:
Hexahydropyrrolo[3,2-*c*]quinolin-2-ones
Hexahydropyridino[3,2-*c*]quinolin-2-ones
Aza-Diels–Alder reactions
Three-component
Cyclic enamides

ABSTRACT

An efficient synthesis of hexahydropyrrolo[3,2-*c*]quinolin-2-ones and hexahydropyridino[3,2-*c*]quinolin-2-ones has been developed in moderate to high yields by one-pot two-step aza-Diels–Alder reactions of *N*-arylimines, formed in situ from anilines and benzaldehydes, with cyclic enamides, formed in situ from 5-hydroxypyrrolidin-2-ones and 6-hydroxypiperidin-2-ones by $BF_3{\cdot}OEt_2$-promoted dehydration in dichloromethane at room temperature. The hexahydropyrrolo[3,2-*c*]quinolin-2-ones were formed as a single *exo*-stereoisomer in most cases and hexahydropyridino[3,2-*c*]quinolin-2-ones were formed as a mixture of *exo*- and *endo*-isomers favoring the *endo*-diastereomer.

The tetrahydroquinoline moiety is present in a number of natural products and many of these molecules have been found to possess a wide spectrum of biological activities, such as antitumoral, antimicrobial, antibacterial, insecticide, analgesic, antipyretic, antiplatelet, and cytotoxic activities.[1] Owing to their relevant biological properties, synthesis of new tetrahydroquinoline derivatives is an active and rewarding research area. Among different ways for constructing tetrahydroquinolines, aza-Diels–Alder reaction between *N*-arylimines and dienophiles is an easy entry to these compounds.[2] Although numerous tetrahydroquinoline derivatives have been afforded by this established method, reports about the construction pyrrolidino- and piperidinoquinolinones are scarce.[3] Pyrroloquinolines form the core structure unit in a number of biologically interesting molecules, such as the natural products martinelline and martinellic acid.[4] Recently, Stevenson reported the synthesis of hexahydropyrrolo[3,2-*c*]quinolines by indium trichloride catalyzed aza-Diels–Alder reactions of *N*-arylimines with *N*-acyl-2,3-dihydropyrrole;[5a] and Lavilla reported the synthesis of hexahydropyridino[3,2-*c*]quinolin-2-ones by $Sc(OTf)_3$ catalyzed aza-Diels–Alder reactions of *N*-arylimines with tetrahydropyrin-2-one.[5b] Despite these achievements, more concise approaches are still required. Recently, we reported a mild procedure for the construction of isoindolo[2,1-*a*]quinolin-11-ones and pyrrolidino[1,2-*a*]quinolin-1-ones by the [4+2] reactions of *N*-acyliminium ions, produced from 3-hydroxy-2-arylisoindol-1-one and 5-hydroxy-1-arylpyrrolidin-2-ones in the presence of $BF_3{\cdot}OEt_2$, with olefins.[6] In this Letter, we report a concise approach to the synthesis of pyrrolidino[3,2-*c*]quinolin-2-ones (**5**) and piperidino[3,2-*c*]quinolin-2-ones (**6**) by the one-pot aza-Diels–Alder reactions of arylimines, formed in situ from the condensation of aniline (**1**) and benzaldehyde (**2**), with cyclic enamides, formed in situ from 5-hydroxypyrrolidin-2-ones (**3**) and 6-hydroxypiperidin-2-ones (**4**) by $BF_3{\cdot}OEt_2$ promoted dehydration (Scheme 1).



Scheme 1. One-pot three-component aza-Diels–Alder reactions.

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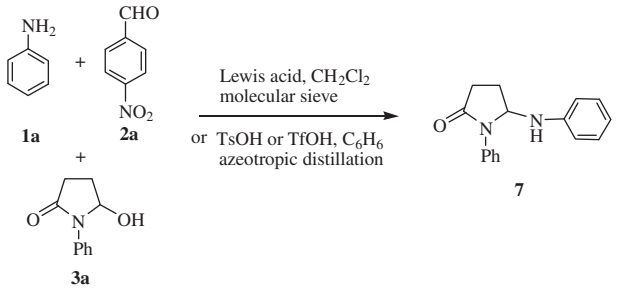
doi:10.1016/j.tetlet.2011.09.021

Initially, we tried to synthesize hexahydropyrrolo[3,2-*c*]quinolin-2-one **5a** by a one-pot reaction of 4-nitrobenzaldehyde, aniline, and 5-hydroxypyrrolidin-2-one in the presence of a dehydration agent and an acid catalyst, hoping that *N*-arylimine could be formed in situ by the condensation of aniline (**1a**) and 4-nitrobenzaldehyde (**2a**) and the cyclic enamide could be generated in situ by the dehydration of **3a** and the subsequent cycloaddition of *N*-arylimine and cyclic enamide catalyzed by the same acid to give the product **5a**. We found, however, the main product was not **5a** but **7**, which appeared to be generated from coupling of **3a** and aniline (**1a**) under catalysis of either Lewis acids in the presence of 4 Å molecular sieves or Brønsted acid with azeotropic distillation dehydration (Scheme 2).

Then, we carried out the reaction by a one-pot two-step procedure: *N*-arylimine was prepared by the condensation of aniline (**1a**) and 4-nitrobenzaldehyde (**2a**) either in the presence of 4 Å molecular sieves in anhydrous dichloromethane (DCM) at room temperature for 2 h or in refluxing benzene (azeotropic distillation) for 2 h until the reaction was completed; next **3a** and an acid were added into the DCM solution and stirring was continued for another 2 h at room temperature or **3a** and an acid were added to the benzene solution and azeotropic distillation was continued for another 2 h. We found that **5a** could be obtained in both cases



Scheme 2. Acid-catalyzed coupling reaction of **1a** with **3a**.

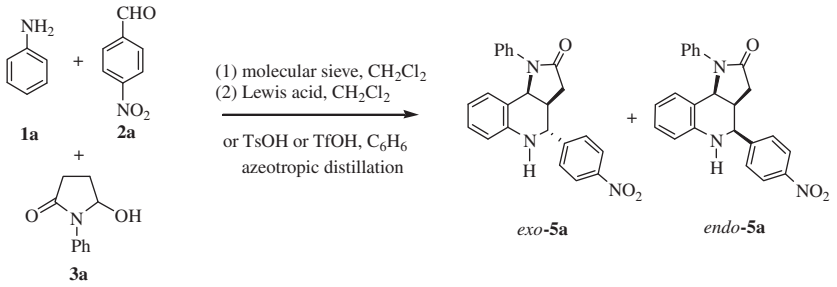
in different yields. Among various acid catalysts examined, such as $BF_3{\cdot}Et_2O$, $Yb(OTf)_3$, $InCl_3$, TsOH and TfOH, $BF_3{\cdot}Et_2O$ was found to give the best result in DCM at room temperature (Table 1). However, in the absence of acid, the reactions did not proceed even after long reaction times (12 h).

Under the optimized conditions, the reaction of *N*-arylimine (formed in situ from anilines and 4-nitrobenzaldehydes in DCM) with **3a** in the presence of 0.8 equiv of $BF_3{\cdot}OEt_2$ for 2 h at room temperature in DCM afforded the corresponding pyrrolidino[3,2-*c*]quinoline-2-ones **5a** as a mixture of *endo*- and *exo*-**5a** isomers in 82% total yield,[7] favoring the *exo*-diastereomer.

The diastereomers could be easily separated by column chromatography on silica gel. In a similar manner, the reactions of other *N*-arylimines (formed in situ from anilines **1a–c** and aromatic aldehydes **2a–d** in DCM) were tested and it was found they could be reacted smoothly with 5-hydroxypyrrolidin-2-ones **3a–c** to afford the corresponding pyrrolidino[3,2-*c*]quinolines **5a–o** in 12–85% yield (Table 2, entries 1–15). In most cases, the product was obtained as a single *exo*-stereoisomer. This high stereoselectivity was much different from the $InCl_3$-catalyzed results in which the ratios of *exo*- and *endo*-isomers were nearly 1:1 as reported by Stevenson.[3a] The results were listed in Table 2. All products were fully identified by ^1H, ^{13}C NMR, and HRMS.[7] The stereoconfiguration of *endo*- and *exo*-**5d** was determined by NOE experiments (Fig. 1)[8] and the structure of *exo*-**5b** was further confirmed by X-ray crystallography (Fig. 2).[9]

Encouraged by the results obtained with 5-hydroxypyrrolidin-2-ones, we turned our attention to 6-hydroxypiperidin-2-one under similar reaction conditions, the produced *N*-arylimines reacted smoothly with 6-hydroxypiperidin-2-ones to produce piperidin[3,2-*c*]quinolin-2-ones **6** in high yields. Similar to the five-membered cyclic enamide intermediates, the reaction of six-membered cyclic enamide intermediates with the preformed *N*-arylimines also gave the products as a mixture of *endo*- and *exo*-isomers. However, the reactions of six-membered cyclic enamide favored *endo*-selectivity as compared with five-membered cyclic enamides (Table 2).

Table 1
Optimization of reaction conditions for synthesis of **5a**



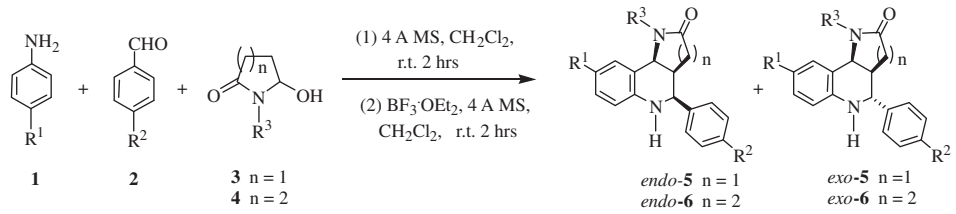
Entry	Solvent/additive	Catalyst	Time (h)	T (°C)	Yield of **5a**[c] (%)
1	CH_2Cl_2/MS[a]	0.5 equiv $BF_3{\cdot}Et_2O$	4	rt	48
2	CH_2Cl_2/MS[a]	0.8 equiv $BF_3{\cdot}Et_2O$	4	rt	82
3	CH_3CN/MS[a]	0.8 equiv $BF_3{\cdot}Et_2O$	4	rt	32
4	CH_2Cl_2/MS[a]	0.8 equiv $Yb(OTf)_3$	12	rt	0
5	CH_2Cl_2/MS[a]	0.8 equiv $InCl_3$	12	rt	0
6	Benzene[b]	0.5 equiv TsOH	4	Reflux	32
7	Benzene[b]	0.5 equiv CF_3CO_2H	4	Reflux	25
8	Benzene[b]	0.5 equiv CF_3SO_3H	4	Reflux	28

[a] 1.1 mmol 4-nitrobenzaldehyde and 1.0 mmol aniline were dissolved in anhydrous DCM, and 0.5 g 4 Å molecular sieves was added. The mixture was stirred at room temperature for 2 h. Then 1.0 mmol **3a** and 0.5–0.8 mmol Lewis acid were added, respectively. The mixture was stirred for 4–12 h.

[b] 1.1 mmol 4-nitrobenzaldehyde and 1.0 mmol aniline were dissolved in benzene. The mixture was refluxed with azeotropic distillation for 2 h. Then 1.0 mmol **3a** and 0.5 mmol acid were added. The mixture was refluxed for another 2 h.

[c] Yield of isolated product based on consumed **3a**.

Table 2
Synthesis of hexahydropyrrolo[3,2-*c*]quinolin-2-ones and hexahydropyridino[3,2-*c*]quinolin-2-ones by one-pot aza-Diels–Alder reaction catalyzed by $BF_3{\cdot}OEt_2$[a]



Entry	Substrate						*n*	Time (h)	Yield[a] (%)		Ratio
		R^1		R^2		R^3					*exo*/*endo*
1	**1a**	H	**2a**	NO_2	**3a**	Ph	1	4	**5a**	82	10/1
2	**1b**	CH_3	**2a**	NO_2	**3a**	Ph	1	4	**5b**	85	1/-
3	**1c**	Cl	**2a**	NO_2	**3a**	Ph	1	6	**5c**	57	1/-
4	**1a**	H	**2b**	CN	**3a**	Ph	1	4	**5d**	72	7/1
5	**1b**	CH_3	**2b**	CN	**3a**	Ph	1	4	**5e**	80	1/-
6	**1c**	Cl	**2b**	CN	**3a**	Ph	1	6	**5f**	37	1/-
7	**1a**	H	**2c**	H	**3a**	Ph	1	4	**5g**	30	1/-
8	**1a**	H	**2a**	NO_2	**3b**	Bn	1	4	**5h**	60	1/-
9	**1b**	CH_3	**2a**	NO_2	**3b**	Bn	1	4	**5i**	80	1/-
10	**1c**	Cl	**2a**	NO_2	**3b**	Bn	1	6	**5j**	45	1/-
11	**1a**	H	**2b**	CN	**3b**	Bn	1	4	**5k**	72	1/-
12	**1b**	CH_3	**2b**	CN	**3b**	Bn	1	4	**5l**	77	1/-
13	**1a**	H	**2c**	H	**3b**	Bn	1	4	**5m**	36	1/-
14	**1b**	CH_3	**2d**	OCH_3	**3b**	Bn	1	4	**5n**	12	1/-
15	**1b**	CH_3	**2a**	NO_2	**3c**	Me	1	4	**5o**	55	1/1
16	**1a**	H	**2a**	NO_2	**4a**	Bn	2	4	**6a**	75	1/1
17	**1b**	CH_3	**2a**	NO_2	**4a**	Bn	2	4	**6b**	84	1/4
18	**1a**	H	**2b**	CN	**4a**	Bn	2	4	**6c**	73	1/1
19	**1b**	CH_3	**2b**	CN	**4a**	Bn	2	4	**6d**	82	1/2
20	**1a**	H	**2c**	H	**4a**	Bn	2	4	**6e**	40	1/1
21	**1b**	CH_3	**2d**	OCH_3	**4a**	Bn	2	4	**6f**	28	1/3

[a] Yield of isolated product based on consumed **3** or **4**.

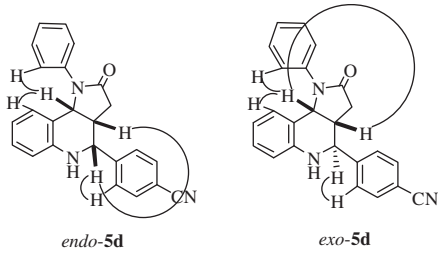


Figure 1. NOE assignments for *endo*- and *exo*-**5d**.

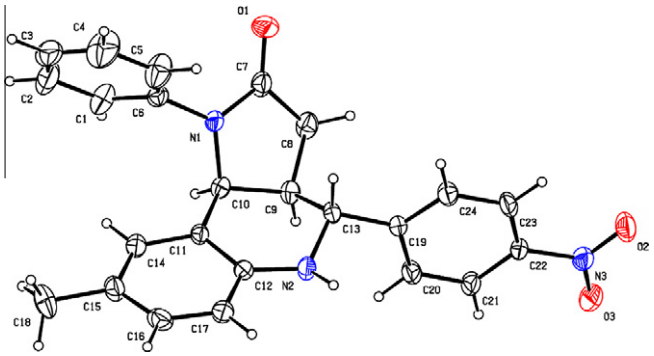
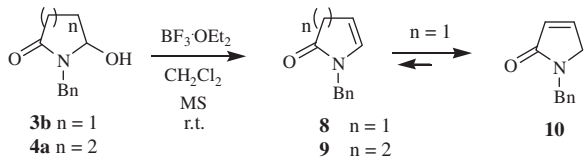
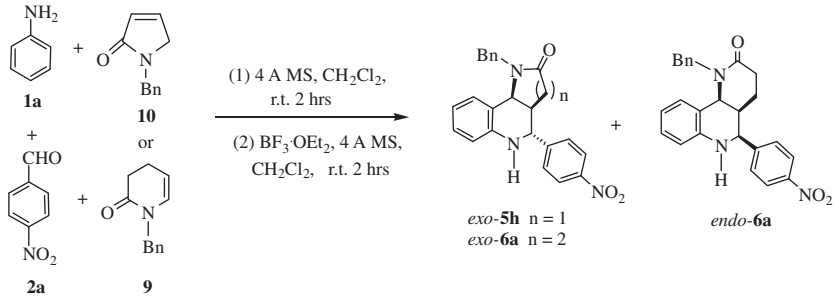


Figure 2. X-ray crystal structure of *exo*-**5b**.

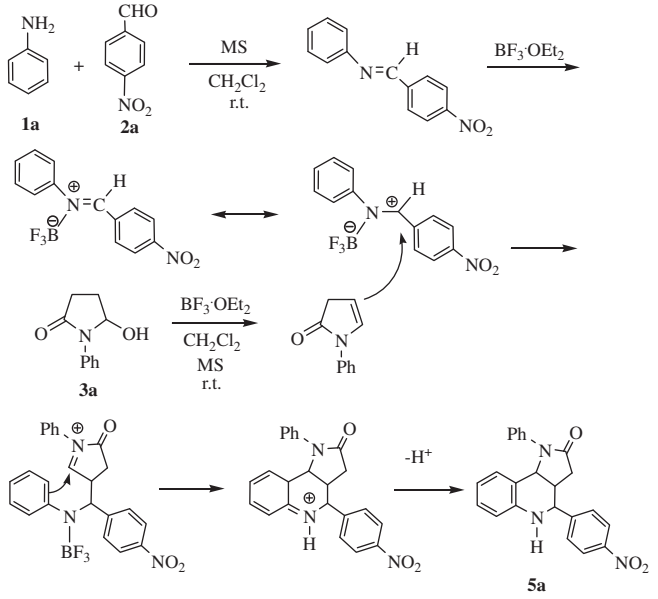
It was also observed from Table 2 that the substituents have great influence to the cycloaddition reactions of *N*-arylimines formed from **1** and **2** with **3** or **4**. The electron-donating group on aniline (R^1 = Me) promoted the reactions and higher yields and *exo*-selectivity of **5** could be reached; In contrast, the electron-attracting group on aniline (R^1 = Cl) retarded the reactions and the yields of **5** decreased; Meanwhile, it was found that the yields of **5b**, **5i**, and **5o** decreased gradually, indicating that R^3 (R^3 = Ph, Bn, and Me) in **3** has great effect on the formation and reactivity of cyclic enamides. On the other hand, R^2 being an electron-withdrawing group like nitro or cyano group in **2** was helpful to both the formation and stability of arylimines, and the yields of **5** and **6** formed from these stable arylimines were relatively higher. Comparatively, reactions of the unstable *N*-phenylimine from **1a** and **2c** (R^1 = R^2 = H) with **3a**, **3b**, or **4a** gave cyclization product **5g**, **5m**, or **6e** in much low yields, especially in the reactions of unstable *N*-arylimine produced from **1b** and electron-donating group-substituted benzaldehyde **2d** with **3b** or **4a**, the yields of the products **5n** and **6f** were decreased greatly. All these results were derived from the formation of the coupling products like **7** from the reactions of *N*-acyliminium



Scheme 3. Dehydration reactions of **3b** and **4a** promoted by $BF_3{\cdot}OEt_2$.



Scheme 4. Reactions of arylimine with cyclic enamides.



Scheme 5. A plausible reaction mechanism of three-component aza-Diels–Alder reaction promoted by $BF_3{\cdot}OEt_2$ in DCM.

ions with anilines produced by the hydrolysis of unstable *N*-arylimine.

In order to confirm the formation of cyclic enamides, the dehydration reactions of **3b** and **4a** promoted by $BF_3{\cdot}OEt_2$ were performed in anhydrous DCM at room temperature. It was found that the cyclic enamides could be produced slowly under these conditions. Differently, the cyclic enamide separated from the reaction of **3b** was 2,5-dihydropyrrol-2-one **10**, but the cyclic enamide separated from the reaction of **4a** was 1,2,3,4-tetrahydropyridin-2-one **9**. (Scheme 3).

Next, the reactions of the separated **9** or **10** with in situ generated arylimine from **1a** and **2a** were examined in DCM at room temperature in the presence of $BF_3{\cdot}OEt_2$ (Scheme 4). It was found that both *exo*-**5h** or *endo*- and *exo*-**6a** could be produced, but the reaction of **10** was much slower (12 h) than the reaction of **9** (2 h). These results indicated that the isomerization of **10**–**8** was reversible but difficult. Moreover, the one-pot reaction of **1a**, **2a** with **10** was also much slower than the one-pot reaction of **1a**, **2a** with **3b** (4 h) (Table 2).

According to these results, a plausible mechanism was proposed for the formation of **5a** by the one-pot reaction of aniline **1a** and benzaldehyde **2a** with **3a** (Scheme 5). Firstly, both *N*-arylimine and cyclic enamide were produced in situ by molecular sieves-promoted condensation of **1a** and **2a**, and by $BF_3{\cdot}OEt_2$-promoted dehydration; then the $BF_3{\cdot}OEt_2$-catalyzed aza-Diels–Alder reaction of the *N*-arylimine and cyclic enamide gave the product **5a**.

In conclusion, we have developed an efficient method for the synthesis of hexahydropyrrolo[3,2-*c*]quinolin-2-ones and hexahydropyridino[3,2-*c*]quinolin-2-ones by one-pot two-step aza-Diels–Alder reactions of *N*-arylimines, produced in situ by the condensation of anilines and benzaldehydes, with the cyclic enamides, produced in situ from $BF_3{\cdot}OEt_2$-promoted dehydration of 5-hydroxypyrrolidin-2-ones and 6-hydroxypiperidin-2-ones. The reaction afforded hexahydropyrrolo[3,2-*c*]quinolin-2-ones as a single *exo*-diastereomer in most cases and afforded hexahydropyridino[3,2-*c*]quinolin-2-ones as a mixture of *endo*- and *exo*-isomers favoring the *endo*-diastereomer.

Acknowledgment

We are grateful to the National Nature Science Foundation of China (Grant No. 20872056) for the financial support.

Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.021.

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7. Synthesis of *exo*- and *endo*-**5a**: Anilines **1a** (1.0 mmol) and aromatic aldehyde **2a** (1.1 mmol) were dissolved in anhydrous CH_2Cl_2 (20 mL), and 0.5 g 4 Å molecular sieves was added. The mixture was stirred at room temperature for 2 h, and 1.0 mmol **3a** and 0.8 mmol $BF_3{\cdot}OEt_2$ were added, respectively. The mixture was stirred for another 2 h. Upon completion monitored by TLC, 10 mL water was added and the resulting mixture was extracted with CH_2Cl_2 (3×20). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was separated by flash chromatography (hexane/acetone 10:1 v/v) to give the products. Compound *enco*-**5a**: mp 244–246 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.36 (t, J = 6.8 Hz, 3H), 7.07 (d, J = 7.2 Hz, 3H), 6.64 (d, J = 8.0 Hz, 1H), 6.48–6.40 (m, 2H), 5.04 (d, J = 5.6 Hz, 1H), 4.38 (d, J = 9.2 Hz, 1H), 4.31 (s, 1H), 2.83–2.79 (m, 1H), 2.72 (dd, J = 7.6, 16.8 Hz, 1H), 2.34 (dd, J = 2.4, 16.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 148.5, 147.9, 137.0, 131.8, 129.5, 129.2, 128.9, 128.2, 127.7, 124.0, 117.9, 116.5, 114.9, 50.5, 56.2, 38.7, and 34.9 ppm. ESI-HRMS: m/z Calcd for $C_{23}H_{19}N_3O_3$+H^+: 385.1500, found 385.1510. Compound *exo*-**5a**: mp 253–255 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.43 (t, J = 8.0 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 7.29 (d, J = 7.2 Hz, 1H), 7.11–7.07 (m, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.61–6.54 (m, 1H), 5.66 (d, J = 8.0 Hz, 1H), 4.75 (d, J = 2.4 Hz, 1H), 3.96 (s, 1H), 3.28–3.21 (m, 1H), 3.08 (dd, J = 11.6, 16 Hz, 1H), 2.02 (dd, J = 8.0, 16.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 147.8, 147.8, 144.3, 138.3, 129.3, 128.9, 127.4, 126.4, 125.6, 124.2, 120.9, 119.6, 116.3, 59.9, 57.5, 40.6, and 30.5 ppm. ESI-HRMS: m/z Calcd for $C_{23}H_{19}N_3O_3$+H^+: 385.1500, found 385.1512.
8. The NOE experiments were also performed for *endo*-**6a**.
9. Crystal data for *exo*-**5b** (recrystallized from acetone–hexane). $C_{24}H_{19}{}_3O_3$, Mr = 399.44, monoclinic, space group $P2$ (1)/n, a = 6.881 (13), b = 15.11 (3), c = 19.58 (4) Å, β = 98.67 (3)°, V = 2013 (7) Å^3, colorless plates, D_c = 1.318 g cm^{-3}, T = 296 (2) K, Z = 4, μ(Mo-K$_\alpha$) = 0.71073 mm^{-1}, $2\theta_{max}$ = 50.4°, 7313 reflections measured, 3581 unique (R_{int} = 0.0741) which were used in all calculations. The final $wR(F2)$ was 0.1416 (for all data), R_1 = 0.0687. CCDC 799818.