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Synthesis of Condensed Tetrahydroisoquinoline Class of Alkaloids by Employing TfOH-Mediated Imide Carbonyl Activation

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Isoquinoline-based polycyclic lactams such as isoindoloisoquinolinones, pyrroloisoquinolinones, and benzo[*a*]quinolizinones were successfully assembled from the corresponding imides by using a TfOH-mediated (TfOH = trifluoromethanesulfonic acid) imide carbonyl activation and cyclization strategy. By employing this simple method, the isoquinoline alkaloids crispine A, trolline/oleracein E, and erythrinarbine were successfully synthesized in racemic form. The reaction of unsymmetrical *N*-phenethylphthalimides with TfOH displayed excellent regioselectivity, which was rationalized by DFT calculations.

Introduction

Condensed heterocycles such as isoindoloisoquinolinone, pyrroloisoquinoline, and benzo[*a*]quinolizine are found in pharmacologically active alkaloids such as nuevamine, trolline, crispine A, erysotramidine, and jamtine as well as in pharmaceuticals such as tetrabenzazine (Figure 1).[1] These classes of molecules display a wide spectrum of biological activities. Some α-alkylated benzo[*a*]quinolizine molecules exhibit excellent pharmacological activity relative to existing drug molecules.[2]

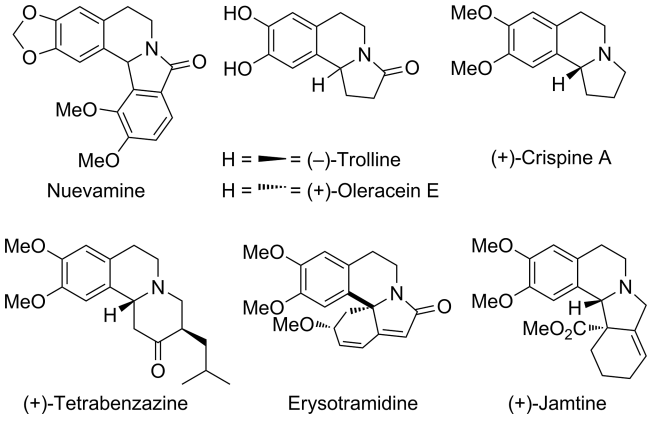

Figure 1. Representative fused tetrahydroisoquinoline (THIQ) alkaloids and pharmaceuticals.

The existence of a large number of biologically active natural and unnatural polycyclic tetrahydroisoquinoline molecules drove many synthetic chemists to develop simple methods to prepare the THIQ skeleton.[3] Some of the existing methods are efficient, but they also have drawbacks such as vigorous reaction conditions, a catalyst/substrate that is not commercially available and difficult to prepare, and specificity toward a particular skeleton. More importantly, the adaptability of some of these methods towards the synthesis of natural products is very limited. With their ease of generation and stability, condensed tetrahydroisoquinoline derivatives can be constructed from *N*-phenethylimides through the formation of a C–C bond between a phenyl carbon atom and the imide carbonyl carbon. Bischler–Napieralski (B–N) reaction conditions have been adopted to synthesize fused isoquinolines from *N*-phenethylimides. For example, these conditions involve heating *N*-phenethylimides at reflux with either $POCl_3$ or PPA/P_2O_5 to furnish cyclic enamides in an uncontrolled manner.[4] The *N*-acyliminium ion and Parham-type cyclizations are other simple and efficient methods that are utilized to convert *N*-phenethylimides into fused tetrahydroisoquinolines in two steps[5] (Scheme 1). The success of these two protocols is attributed to the activation of either the electrophile (*N*-acyliminium ion) or the nucleophile (Parham-type) that is present in the substrate. The former method involves the conversion of the imide into a hydroxyisoindolone prior to the cyclization. The latter one involves the halogenation of the aryl group by using an interhalogen compound followed by a cyclization that is facilitated by butyllithium.

We recently reported our initial work towards developing a BBr_3- or TfOH-promoted imide carbonyl group activation strategy for the construction of fused isoquinolinone and β-carboline skeletons from the corresponding imides.[6] These studies mainly dealt with the conversion of activated and some selected *N*-phenethylphthalimides, -succinimides,

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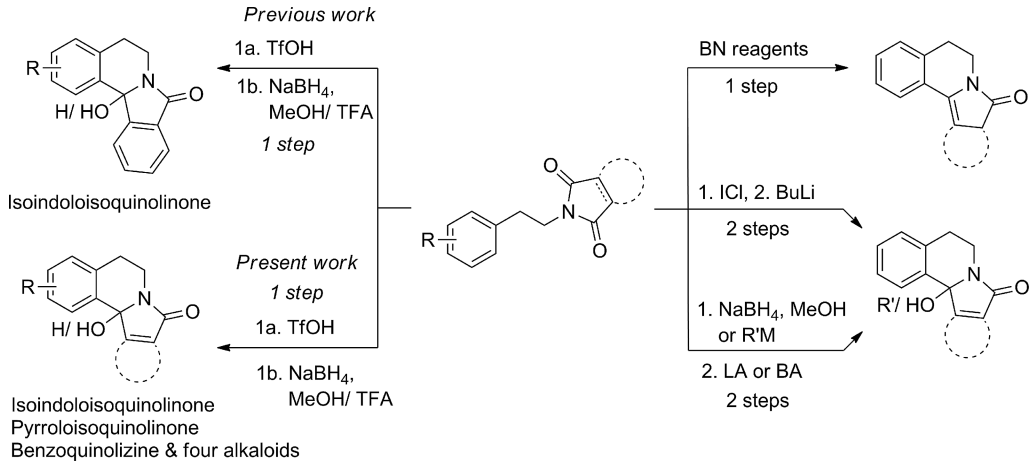


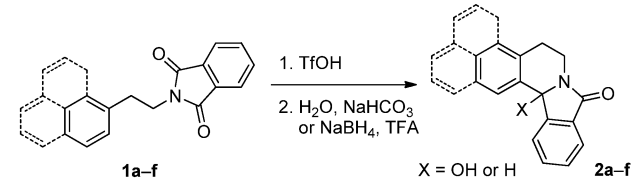
Scheme 1. Comparison of the Bischler–Napieralski reaction, the Parham-type cyclization, and the *N*-acyliminium ion cyclization with the present method (TfOH = trifluoromethanesulfonic acid, TFA = trifluoroacetic acid, M = metal, LA = Lewis acid, BA = Brønsted acid).

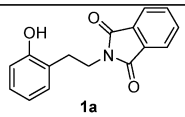
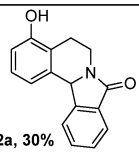
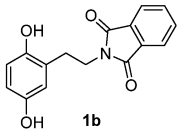
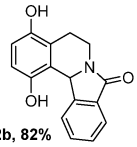
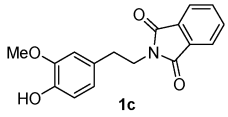
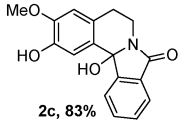
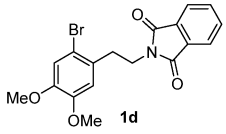
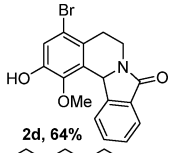
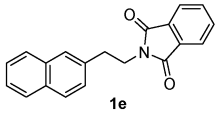
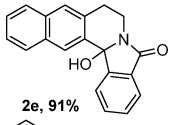
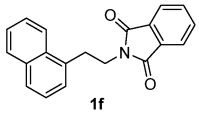
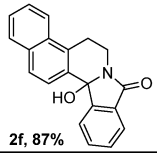
and -glutarimides into the corresponding fused isoquinolinones by using BBr_3. Later, the same reaction was successfully carried out with variety of *N*-phenethylphthalimides by using TfOH.[6b] To further justify the versatility of this methodology towards the synthesis of unique fused isoquinoline motifs, we plan to explore the cyclization of *N*-phenethylphthalimides, *N*-naphthylethylphthalimides, *N*-phenethylsuccinimides, and *N*-phenethylglutarimides into the corresponding cyclized products. Finally, the efficiency of this methodology is demonstrated by the successful short synthesis of alkaloids that contain the tetrahydroisoquinoline skeleton such as crispine A, trolline/oleracein E, and erythrinarbine.

Results and Discussion

So far, the methoxy-substituted *N*-phenethylphthalimides and *N*-[2-(3-indolylethyl)]phthalimide, -succinimide, and -glutarimide derivatives have successfully generated the condensed heterocyclic skeletons under the influence of TfOH. However, there are alkaloids such as trolline/oleracein E and erythrinarbine that have phenolic OH groups. Hence, we decided to examine the compatibility of the phenethyl moiety with a free OH group in this cyclization reaction. The substrate *N*-[2-(2-methoxyphenyl)ethyl]-phthalimide failed to deliver the cyclized product upon treatment with TfOH even at an elevated temperature, whereas *N*-[2-(3,4-dihydroxyphenyl)ethyl]phthalimide furnished the corresponding cyclized product in presence of TfOH. This observation prompted us to examine the cyclization reaction of *N*-[2-(2-hydroxyphenyl)ethyl]phthalimide (**1a**) with TfOH instead of the cyclization of *N*-[2-(2-methoxyphenyl)ethyl]phthalimide. Accordingly, imide **1a** was treated with TfOH at 70 °C under neat conditions, which delivered the corresponding cyclized product **2a** in 30% yield (Table 1, Entry 1). Similarly, the substrate *N*-[2-(2,5-dihydroxyphenyl)ethyl]phthalimide (**1b**) furnished the corresponding cyclized product **2b** in 82% yield (Table 1, Entry 2). The *N*-[2-(3-methoxy-4-hydroxyphenyl)ethyl]phthalimide (**1c**), which is derived from vanillin, underwent the cyclization in the presence of TfOH followed by quenching the reaction with a mild base (equal of $NaHCO_3$ with respect to TfOH) to deliver hydroxy lactam **2c** in 83% yield. The presence of the existing acidic phenolic group did not affect the acid-sensitive hydroxy lactam unit (Table 1, Entry 3). Upon cyclization, *N*-[2-(3-methoxyphenyl)ethyl]-phthalimide and *N*-[2-(3,4-dimethoxyphenyl)ethyl]phthalimide led to the cyclized compounds, in which the new C–C bond was established between the imide carbonyl carbon and the phenyl carbon atom that is *para* to the methoxy group, even though the *ortho* position was available. To direct the cyclization at the *ortho* position (*ortho* to the directing methoxy group), *N*-[2-(2-bromo-4,5-dimethoxyphenyl)-ethyl]phthalimide (**1d**) (with a bromo at the *para* position with respect to the directing methoxy group and thus blocking that carbon for cyclization) was prepared. Imide **1d** failed to furnish the cyclized product in presence of TfOH at room temperature, but under neat conditions at reflux in the presence of TfOH, **1d** delivered the expected *ortho*-cyclized product **2d** in 64% yield (Table 1, Entry 4). However, the methyl group of the methoxy group at C-4 was cleaved during the process. To further diversify the structural skeletons, we decided to examine the naphthyl group as the π-nucleophile in this cyclization reaction. Accordingly, the *N*-[2-(2-naphthyl)ethyl]phthalimide (**1e**) was subjected to the cyclization by using TfOH at room temperature, and the aqueous workup delivered cyclized product **2e** in 91% yield (Table 1, Entry 5 and Figure 2). Because of steric reasons, cyclization occurred at the C-3 position instead of more reactive C-1 position of the naphthyl ring. Also, *N*-[2-(1-naphthyl)ethyl]phthalimide (**1f**) smoothly delivered the steroidal-type skeleton hydroxy lactam **2f** in 87% yield (Table 1, Entry 6; Figure 2).

Table 1. Synthesis of isoindoloisoquinolinones and isoindolonaphthaquinolinones.



Entry	Imide	Time [h]	Isoindoloisoquinolinone[d]
1[a]	 1a	48	 2a, 30%
2[b]	 1b	12	 2b, 82%
3[c]	 1c	0.5	 2c, 83%
4[b]	 1d	12	 2d, 64%
5[c]	 1e	12	 2e, 91%
6[c]	 1f	12	 2f, 87%

[a] (1) imide (0.5 mmol), TfOH (8 equiv.), 70 °C for 48 h; (2) $NaBH_4$ (2 mmol)/TFA (1 mL), 15 min. [b] (1) imide (0.5 mmol), TfOH (6 equiv.), 70 °C for 12 h; (2) $NaBH_4$ (2 mmol)/TFA (1 mL), 15 min. [c] (1) imide (0.5 mmol), TfOH (2 mmol, 4 equiv.), CH_2Cl_2 (15 mL), 0 °C to room temp., 0.5 or 12 h; (2) H_2O, $NaHCO_3$ (2 mmol). [d] Yield of isolated product.

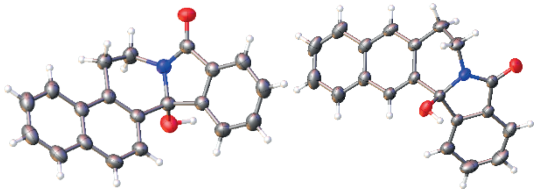
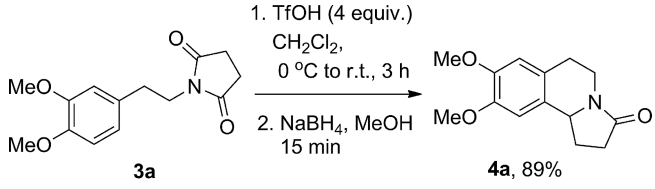


Figure 2. ORTEP diagrams for compounds **2e** and **2f** with 50% probability level.

Synthesis of Pyrroloisoquinolinone and Benzo[*a*]quinolizinone Derivatives

Pyrroloisoquinolines and benzo[*a*]quinolizinones, which are fused tricyclic subunits frequently encountered in isoquinoline alkaloids, are known to have various therapeutic uses. The wide substrate scope for the Brønsted acid assisted imide carbonyl activation of *N*-phenethylphthalimides motivated us to exploit this strategy to synthesize pyrroloisoquinolinones from *N*-phenethylsuccinimides. Thus, the synthesis of pyrroloisoquinolinone began by examining the reaction of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-succinimide (**3a**) with 4 equiv. of TfOH at 0 °C to room temperature. After 3 h, the generated fused cyclic iminium ion (monitored by TLC) was reduced in situ by using $NaBH_4$/MeOH to deliver tricyclic lactam **4a** in 89% yield (Scheme 2 and Figure 3).



Scheme 2. Cyclization and reduction of imide **3a**.

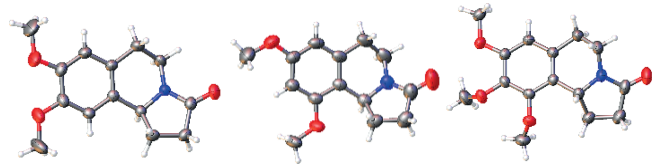
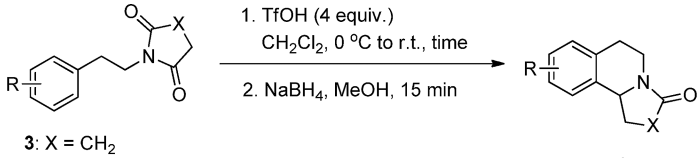


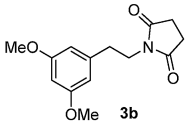
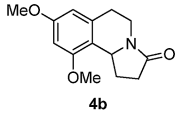
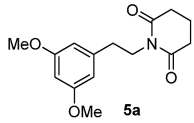
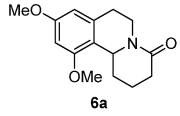
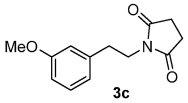
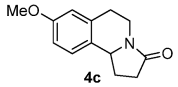
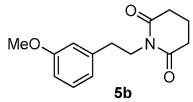
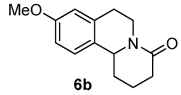
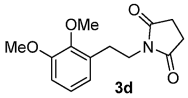
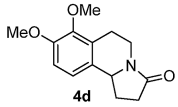
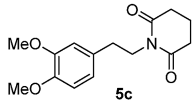
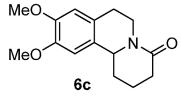
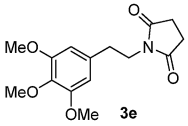
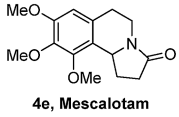
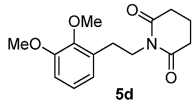
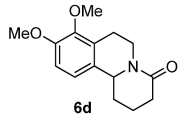
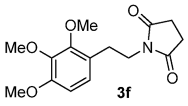
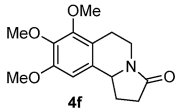
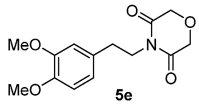
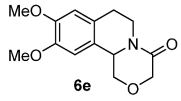
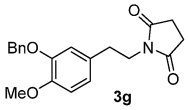
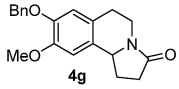
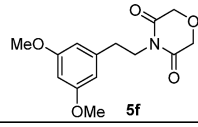
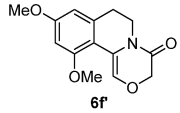
Figure 3. ORTEP diagrams for the compounds **4a**, **4b** and **4e** with 50% probability level.

Encouraged by this result, various methoxy-substituted *N*-phenethylsuccinimides **3b**–**3g** were subjected to this cyclization/reduction sequence to generate pyrroloisoquinolinone derivatives **4b**–**4g** (Table 2, Entries 1–6). As expected, all of the imides **3b**–**3g** produced good yields of products **4b**–**4g**. Imide **3e** underwent cyclization followed by an in situ reduction to deliver the alkaloid mescalotam **4e** (Table 2, Entry 4 and Figure 3), which was originally isolated from *Lophophora williamsii*.[7] The time required for the conversion of the imide into the fused cyclic iminium ion depended on the positions of the methoxy groups that are present in the benzene ring of the phenethyl moiety. For example, the conversion of *N*-[2-(3,4-dimethoxyphenyl)-ethyl]succinimide (**3a**) and *N*-[2-(2,3,4-trimethoxyphenyl)-ethyl]succinimide (**3f**) into lactams **4a** and **4f** required 3 and 8 h respectively, whereas *N*-[2-(3,5-dimethoxyphenyl)ethyl]-succinimide **3b** furnished lactam **4b** in 1 h (Figure 3). The slow reactivities of **3a** and **3f** may result from the presence of the 2-methoxy, 4-methoxy, or both groups on the benzene ring of the phenethyl moiety, which would inductively deactivate the aromatic carbon involved in C–C bond formation. Imide **3g**, which contains the benzyloxy and methoxy groups also furnished cyclized product **4g** in 46% yield.

The construction of the benzo[*a*]quinolizinone skeleton was also realized by using TfOH. Methoxy-substituted glutarimides **5a**–**5d** smoothly underwent cyclization at 0 °C followed by an in situ reduction at room temperature to deliver the benzo[*a*]quinolizinone derivatives **6a**–**6d** in good

Table 2. Synthesis of pyrroloisoquinolinone and benzo[*a*]quinolizinone derivatives.[a]



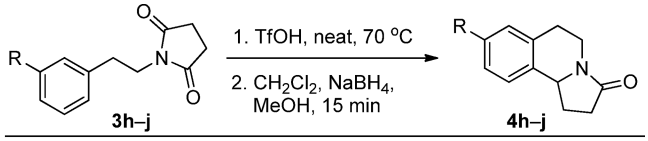
Entry	Substrate	Time [h]	Product	Yield [%][b]	Entry	Substrate	Time [h]	Product	Yield [%][b]
1	 **3b**	1	 **4b**	87	7	 **5a**	1	 **6a**	84
2	 **3c**	1	 **4c**	89	8	 **5b**	1	 **6b**	82
3	 **3d**	1	 **4d**	65	9	 **5c**	3	 **6c**	87
4	 **3e**	1	 **4e, Mescalotam**	81	10	 **5d**	3	 **6d**	83
5	 **3f**	8	 **4f**	73	11	 **5e**	1	 **6e**	40
6	 **3g**	1	 **4g**	46	12	 **5f**	1	 **6f′**	74

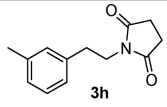
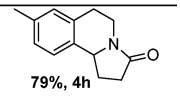
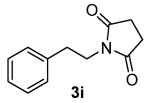
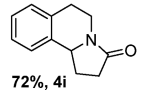
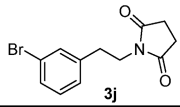
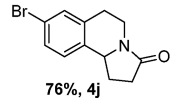
[a] Reagents and conditions: (1) imide (0.5 mmol), CH_2Cl_2 (15 mL), TfOH (2 mmol), 0 °C to room temp., (2) $NaBH_4$ (2 mmol)/MeOH (3 mL), 15 min. [b] Yield of isolated product.

yields (Table 2, Entries 7–10). The substrate *N*-[2-(3,4-dimethoxyphenyl)ethyl]diglycolimide (**5e**) furnished the expected cyclized product **6e** in 40% yield, and the ether linkage of the imide was not affected by the reaction conditions. On the other hand, *N*-[2-(3,5-dimethoxyphenyl)ethyl]diglycolimide (**5f**) gave tricyclic enamide **6f′** exclusively in 74% yield. A change in the reduction temperature and the use of an excess amount of reducing agent did not affect the yield of the enamide.

To examine the electronic effect of the internal phenyl nucleophile towards this cyclization process, the *N*-phenethylsuccinimides that contained a methyl group (i.e., **3h**), were unsubstituted (i.e., **3i**), or contained a weakly deactivating bromo group (i.e., **3j**) were treated with TfOH. Imides **3h**–**3j** failed to generate the fused cyclic iminium ion at 0 °C to room temperature, which proved that the nucleophilicity of these internal phenyl nucleophiles was insufficient to undergo a reaction with the Brønsted acid activated imide carbonyl group. Instead, upon treatment with an excess amount of TfOH at an elevated temperature under neat conditions, imides **3h**–**3j** successfully produced cyclized products **4h**–**4j** (Table 3). For example, heating the

Table 3. Cyclization of unactivated *N*-phenethylsuccinimides.[a]



Entry	Imide	Time [h]	TfOH (equiv.)	Product[b]
1	 **3h**	12	6	 **79%, 4h**
2	 **3i**	30	8	 **72%, 4i**
3	 **3j**	48	10	 **76%, 4j**

[a] Reagents and conditions: (1) imide (0.5 mmol), TfOH, neat at 70 °C, (2) CH_2Cl_2 (10 mL), $NaBH_4$ (2 mmol), MeOH (2.5 mL), 15 min. [b] Yield of isolated product.

methyl-substituted *N*-phenethylsuccinimide **3h** with TfOH (6 equiv.) at 70 °C for 12 h followed by a reduction using $NaBH_4$/MeOH produced the expected cyclized product in 79% yield. The unsubstituted and bromo-substituted *N*-phenethylsuccinimides **3i** and **3j** produced cyclized products **4i** and **4j** in 72 and 76% yield, respectively. However, the reactions of unsubstituted and bromo-substituted substrates required 8 and 10 equiv. of TfOH, respectively.

To expose the utility of this simple and single step conversion of *N*-phenethylimides into fused tetrahydroiso quinoline motifs by using a Brønsted acid, the synthesis of alkaloids that contain either the isoindoloisoquinolinone or the pyrroloisoquinolinone structure, two important classes of THIQ skeletons, have been successfully performed.

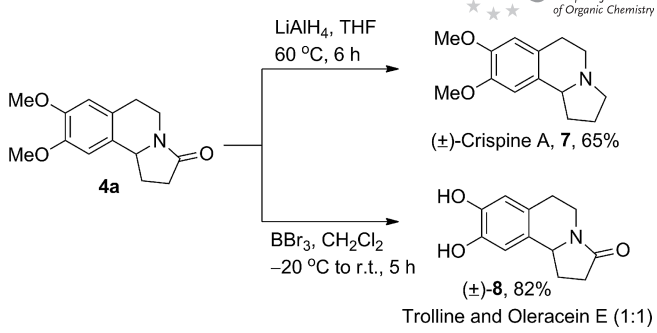
Synthesis of Pyrroloisoquinoline Alkaloids: (±)-Crispine A, (±)-Trolline, and (±)-Erythrinarbine

Zhao et al. isolated the pyrroloisoquinoline alkaloid (+)-crispine A along with four other alkaloids from the leaves of the Chinese folk medicinal plant *Carduus crispus*, a popular invasive plant found in Asia and Europe.[8] This alkaloid exhibits antitumor activity against SKOV3, KB, and HeLa human cancer cell lines. As a result of its potent antitumor activity, twenty nine synthetic strategies have been developed for the synthesis of racemic and optically pure crispine A.[9]

Wang et al. isolated the dihydroxypyrroloisoquinolinone alkaloid (–)-trolline from the flowers of *Trollius chinensis*.[10a] Zhao et al. isolated the same compound from the flowers of *Salsola collina* and named it salsoline A.[10b] Xiang et al. isolated the (+)-form of the same compound, named *R*-(+)-oleracein E, from *Portulaca oleracea*.[10c] Oleracein E is a strong antioxidant,[11] and trolline has appreciable antibacterial activity and moderate antiviral activity.[10a] To date, there have been five synthetic strategies reported for the synthesis of racemic and optically pure trolline/oleracein E.[3x,9j,9v,12]

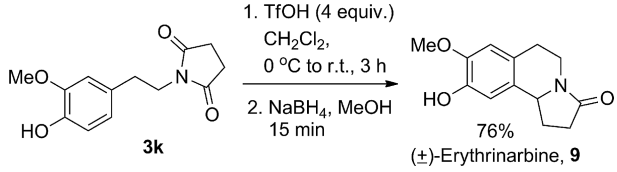
The structural features of the alkaloids crispine A and trolline/oleracein E reveal that these molecules can be assembled from the common intermediate **4a**. Pyrroloisoquinolinone **4a** was easily prepared in 89% yield from *N*-phenethylsuccinimide **3a** by applying the TfOH-mediated cyclization protocol (Scheme 2). The lithium aluminum hydride reduction of the **4a** smoothly delivered the pyrroloisoquinoline alkaloid (±)-crispine A in 63% yield, whereas, under demethylation conditions, precursor **4a** gave 1:1 mixture of trolline and oleracein E in 82% yield (Scheme 3).

Yu et al. reported the isolation and structural elucidation of a new pyrroloisoquinolinone alkaloid (±)-erythrinarbine (**9**) from the stem of *Erythrina arborescens*, which belongs to the *Erythrina* genus of the Papilionaceae family[13] and is widely found in the tropical and subtropical regions of the world as well as in the south and southwest regions of China. As a Chinese folk medicine, the root and stem of *E. arborescens* are used to treat rheumatism and dysentery. The synthesis of this biologically active molecule has not



Scheme 3. Synthesis of crispine A and trolline/oleracein E mixture (THF = tetrahydrofuran).

been reported thus far. Hence, we have employed the Brønsted acid assisted cyclization of the appropriate succinimide to synthesize erythrinarbine. First, the required imide **3k** was prepared in four simple steps from vanillin in 85% overall yield. The resulting *N*-[2-(3-methoxy-4-hydroxyphenyl)ethyl]succinimide (**3k**) smoothly underwent cyclization in the presence of TfOH. The reduction of the iminium ion intermediate by treatment with $NaBH_4$/MeOH delivered the alkaloid (±)-erythrinarbine (**9**) in 76% yield (Scheme 4).



Scheme 4. Synthesis of (±)-erythrinarbine.

The spectroscopic data of synthesized erythrinarbine were in good agreement with those reported of the isolated compound. The structure of the prepared erythrinarbine was further confirmed by single-crystal X-ray analysis (Figure 4).

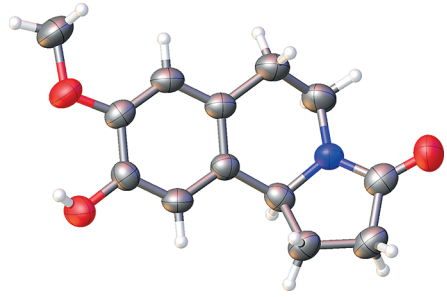
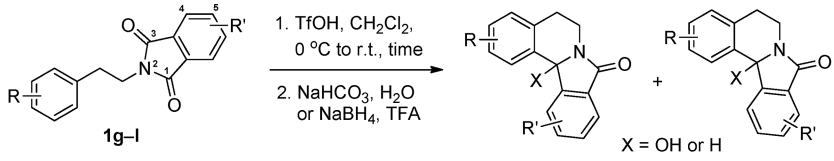


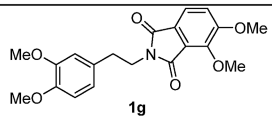
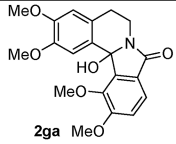
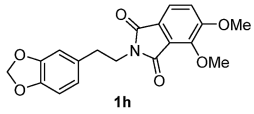
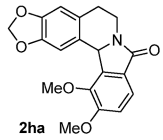
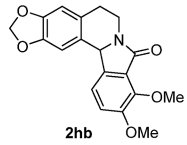
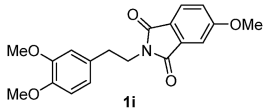
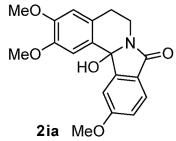
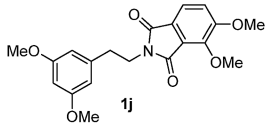
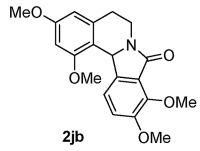
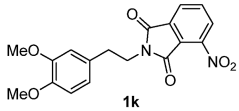
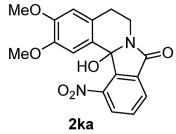
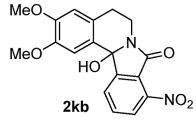
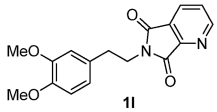
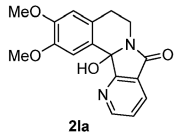
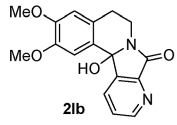
Figure 4. ORTEP diagram for compound **9** with 50% probability level.

Regioselective Cyclization of Unsymmetrical Phenethylphthalimides

After a successful cyclization step, the resulting symmetrical *N*-phenylethylphthalimides were produced as one regioisomeric product. However, the incorporation of substituents on the phthalimide moiety may potentially lead to

Table 4. Cyclization of unsymmetrical *N*-phenethylphthalimides.[a]



Entry	Substrate	Time [h]	Product **2** series **a**	Product **2** series **b**	Yield [%][b]
1[a]	 **1g**	0.5	 **2ga**		85
2	 **1h**	0.5 & 36	 **2ha**	 **2hb**	0 °C 86 (52:48) -78 °C 92 (88:12)
3	 **1i**	0.5	 **2ia**		89
4[c]	 **1j**	0.5		 **2jb**	83
5	 **1k**	0.5	 **2ka**	 **2kb**	86 (62:38)
6	 **1l**	0.5	 **2la**	 **2lb**	**2la**: 48 **2lb**: 46

[a] (1) imide (0.5 mmol), TfOH (2 mmol, 4 equiv.), CH_2Cl_2 (15 mL), 0 °C to room temp., 30 min, (2) H_2O, $NaHCO_3$ (3 mmol) or $NaBH_4$ (2 mmol)/TFA (1 mL), 15 min. [b] Yield of isolated product.

two regioisomeric products. For example, the tetramethoxy-substituted phenethylphthalimide (**1g**) underwent cyclization regioselectively in the presence of TfOH to deliver the single isomer **2ga** in 85% yield (Table 4, Entry 1). However, the nuevamine precursor **1h** with a methylenedioxy unit on the nucleophilic aryl portion furnished the two possible regioisomers, nuevamine (**2ha**) and isonuevamine (**2hb**), in equal ratio at 0 °C. When the same reaction was carried out at –78 °C, the quantity of nuevamine **2ha** increased relative to isonuevamine (**2hb**, Table 4, Entry 2). This regioselectivity difference prompted us to undertake a systematic study of the regioselective cyclization of unsymmetrical *N*-phenethylphthalimides. By examining how functional groups and their positions affect the regioselectivity of the reaction, we could further fine-tune the cyclization conditions for the selective synthesis of particular regioisomers.

Hence, we initiated our investigation of regioselective cyclizations that incorporate electronically complementary functional groups such as methoxy and nitro groups into the phthalimide unit. These substrates were subjected to the cyclization reaction in the presence of TfOH, and the results are reported in Table 4. Imide **1i** with one methoxy group on the phthalimide moiety (at the 5-position) displayed a similar regioselectivity to that of imide **1g** and yielded only **2ia** (Table 4, Entry 3; Figure 5). A complementary regioselective cyclization was observed when imide **1j** was treated with TfOH followed by a reduction using $NaBH_4$/TFA. The formation of only **2jb** may occur because of the steric congestion in the transition state between the methoxy group on phenyl ring of phenethyl moiety and the methoxy group on the phthalimide unit. Phthalimide **1k** that contained an electron-withdrawing nitro group on the

imide portion furnished a mixture of the two regioisomers **2ka** and **2kb** (**2ka**/**2kb**, 62:38) in 86% yield (Table 4, Entry 5; Figure 5). Similarly, upon treatment with TfOH, pyridine imide **1l** also delivered the two regioisomers **2la** and **2lb** (Table 4, Entry 6).

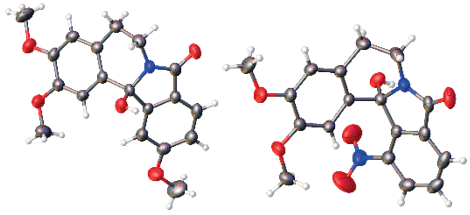


Figure 5. ORTEP diagrams for the compounds **2ia** and **2ka** with 50% probability level.

Although imides **1g** and **1i** structurally differ on the phthalimide portion, both exhibited the same regioselectivity. Under TfOH-assisted cyclization, the C–C bond was established between the phenyl carbon atom and the imide carbonyl carbon proximal to the methoxy group(s) of the phthalimide portion. In the case of imide **1j**, a positional isomer of **1g**, the phenyl nucleophile approaches the carbonyl carbon distal to methoxy group to afford the opposite regioselectivity. The regioselectivity that was observed with the cyclizations of imides **1g** and **1i** (each with a methoxy group *para* to the cyclizing carbon atom) reveals that an electron-donating group (e.g., methoxy) on the phthalimide unit exclusively favors the nucleophile to approach the carbonyl carbon proximal to the methoxy group(s). However, if there is steric congestion from a substituent, as in the case of **1j** with the methoxy group that was *ortho* to the position of cyclization, this will ultimately favor the nucleophile to approach the steric-free distal imide carbonyl carbon. Comparatively, a more reactive nucleophile, such as that with a methylenedioxy-fused benzene group (i.e., **1h**) or that with an electron-withdrawing group (e.g., the nitro group) present in the phthalimide portion, favors the formation of a mixture of regioisomers with a slight excess amount of the proximal regioselective product. When the reaction was conducted below 0 °C, the nucleophile approached the carbonyl group that was proximal to the methoxy group on the phthalimide unit, which led to the corresponding regioisomeric product. Hence, nuevamine was formed as a major product relative to isonuevamine when the reaction was carried out at –78 °C.

To understand the mechanistic reasoning behind this regioselectivity and the effect of the functional groups during cyclization, we carried out computational studies by using B3LYP/6-31G(d) level of theory, which is commonly employed for general chemical reactions. Hence, B3LYP/6-31G(d) geometry optimizations were performed in Gaussian 09 for the model systems in the gas phase.[14] Frequency calculations were performed to verify the nature of all the stationary points as either minima or transition states and to provide zero-point energy corrections. The geometries from the gas phase calculations were used directly, as it is assumed that solvation would not dramatically change the geometries. Two model systems, namely, the nuevamine precursor 2-[2-(1,3-benzodioxol-5-yl)ethyl]-4,5-dimethoxy-1*H*-isoindole-1,3-(2*H*)dione (**1h**) and 2-(3,4-dimethoxyphenethyl)-4,5-dimethoxyisoindoline-1,3-dione (**1g**) were chosen for the theoretical study.

According to Mulliken atomic charge analysis, the carbonyl carbon atom that is proximal to methoxy side of imide **1h** has more positive character than the distal carbonyl carbon (Figure 6). Protonation of carbonyl oxygen atom (at C-3) that is proximal to the methoxy group is 6.90 kcal/mol more stable than the protonation of carbonyl oxygen (at C-1) that is distal to the methoxy group. Because of the probable existence of intramolecular hydrogen bonding between

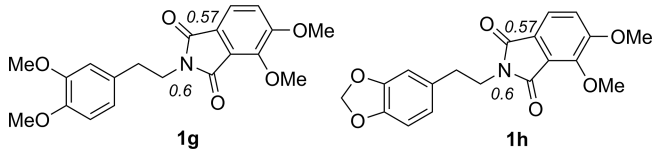


Figure 6. Mulliken charge distribution of imide **1g** and **1h**.

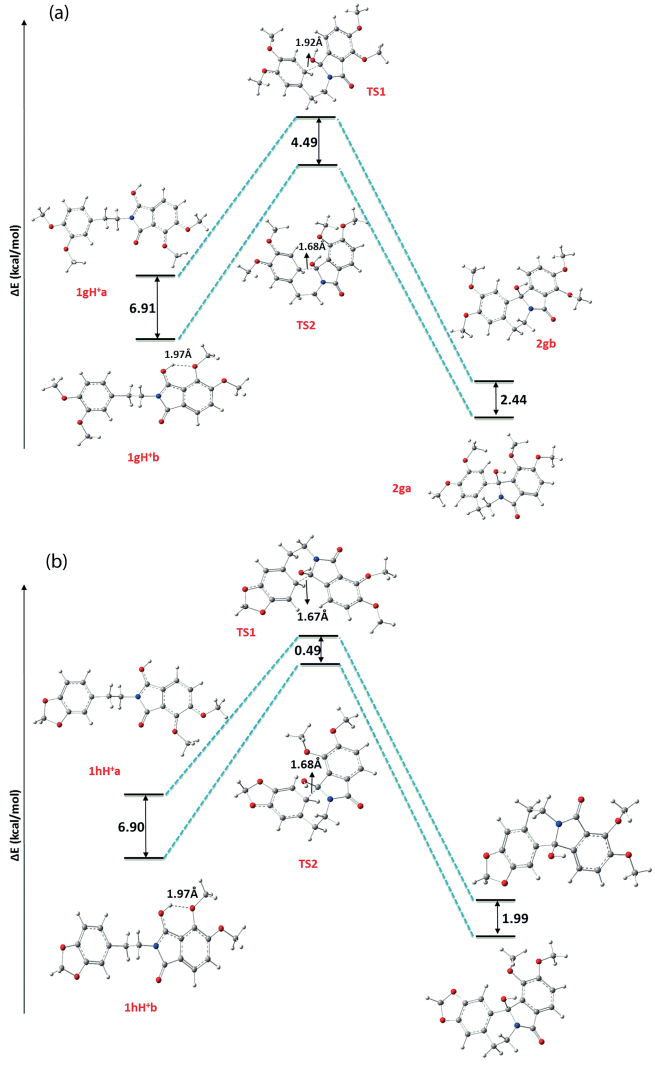


Figure 7. Computed geometries and transition states of imide **1g** (top) and **1h** (bottom).

the protonated carbonyl oxygen and the methoxy group, the protonation of the carbonyl oxygen (at C-3) proximal to the methoxy group is favored. Similarly, the protonation of imide **1g** also occurs at the carbonyl oxygen on the methoxy side, which is 6.91 kcal/mol more stable.

The two protonated species **1hH$^+$a** and **1hH$^+$b** of imide **1h** undergo the intramolecular cyclization through the chair-like transition states TS1 and TS2, respectively. The energy difference between TS1 and TS2 is only 0.49 kcal/mol, and, hence, both regioisomers are formed in equal amounts at 0 °C (Figure 7, bottom).

Similarly, the two protonated species **1gH$^+$a** and **1gH$^+$b** of imide **1g** also undergo the intramolecular cyclization through chair-like transition states TS1 and TS2, respectively. Among these two transition states, TS2 is 4.49 kcal/mol more stable than TS1. This large energy difference leads to the regioselective cyclization of **1g** to generate only one regioisomeric product under the same experimental conditions (Figure 7, top).

Conclusions

The activation of the imide carbonyl group of the *N*-phenethylimides by using TfOH facilitated the intramolecular cyclization with the internal aryl nucleophile to deliver fused tetrahydroisoquinoline derivatives such as isoindoloisoquinolinones, pyrroloisoquinolinones, and benzo[*a*]quinolizinones. The substrate scope of this metal-free protocol is excellent, and, hence, both activated and unactivated *N*-arylethylimides underwent cyclization in the presence of TfOH. Fused tetrahydroisoquinoline alkaloids such as nuevamine, crispine A, trolline, and mescalotam were successfully synthesized by a short route using the Brønsted acid assisted imide carbonyl group activation strategy. The overall yields are comparatively better than those of reported methods. We have also for the first time accomplished the total synthesis of the erythrinarbine alkaloid by using the cyclization/reduction sequence as the key step. The systematic investigation of the regioselective cyclization of unsymmetrial *N*-phenethylphthalimides by both experimental and computational methods was disclosed for the first time.

Experimental Section

General Methods: Melting points were measured with an EZ Melt (Stanford Research Systems, USA). Infrared spectra were recorded on a Thermo Nicolet 6700 FT-IR spectrophotometer by using potassium bromide thin films. The IR data are reported in absorption frequencies (cm^{-1}). Mass spectra and GC–MS, were recorded on a Varian GC–MS (CP-3800/Saturn 2200). LDI-MS (LDI = laser desorption/ionization) were recorded on an ABI Voyager DE-STR mass spectrometer. HRMS were measured by micromass Q-TOF (ESI-HRMS). The ^{1}H and ^{13}C NMR spectroscopic data were recorded with a Bruker AVANCE 400 spectrometer. All NMR spectra were recorded at room temperature, and either $CDCl_3$ or [D$_6$]DMSO was used as the solvent with TMS as an internal standard. The chemical shifts are expressed in δ (ppm) downfield from the signal of the TMS. Coupling constant (J) values are given in Hz. The multiplicities of the NMR signals are reported as: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), td (triplet of doublet), or br. s (broad singlet). X-ray crystal data were collected on an Oxford Diffraction Xcalibur diffractometer with Mo-K_α radiation (λ = 0.71073 Å). The empirical absorption correction by using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm, was applied. The structure solution and refinement were performed with SHELX-97.[15] All solvents that were used for the reactions were distilled according to standard procedures.[16] Dry dichloromethane was obtained by distillation over calcium hydride. The substituted phenethylamines were prepared from the corresponding aldehydes by three simple synthetic steps that involved a nitroaldol condensation and a reduction of the double bond and nitro group.[17] The reagents TfOH, phenethylamine, and 3,4-dimethoxyphenethylamine from Aldrich were used without further purification. Column chromatography was performed on Merck silica gel (100–200 mesh). The developed TLC plates (Merck 60 F_{254} precoated silica plates) were visualized by using phosphomolybdic acid stain, permanganate stain, and UV light.

General Procedure for TfOH-Mediated Cyclization at Higher Temperature and Reduction at Room Temperature: An oven-dried two-neck round-bottom flask that had a septum in the side arm was cooled to room temperature under a steady stream of nitrogen. The flask was charged with a stir bar, the substrate (0.5 mmol), and TfOH. The contents were heated at 70 °C. After the stipulated time, the contents were warmed to room temperature, and CH_2Cl_2 (10 mL) and $NaBH_4$ (2 mmol) were added followed by TFA (1 mL). The resulting solution was stirred until the color disappeared. (Additional $NaBH_4$ and TFA were used if the color persisted for a long time). The crude mixture was concentrated to dryness under reduced pressure. The solid residue was dissolved in dichloromethane (20 mL), and the insoluble material was removed by filtration. The filtrate was dried with anhydrous Na_2SO_4 and filtered. The solvent was evaporated under vacuum, and the crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 60:40).

4-Hydroxy-5,12b-dihydro-6*H*-isoindolo[1,2-*a*]isoquinolin-8-one (2a): By following the general procedure, imide **1a** (133 mg, 0.5 mmol) furnished the cyclized product **2a** (37 mg, 30% yield) as a colorless solid; m.p. 94 °C. IR (KBr): $\tilde{\nu}$ = 3328, 1663, 1624, 1510 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.85 (m, 2 H), 7.62–7.58 (m, 1 H), 7.49 (t, J = 7.6 Hz, 1 H), 7.28–7.26 (m, 1 H), 7.16 (t, J = 7.9 Hz, 1 H), 6.72 (d, J = 7.9 Hz, 1 H), 5.69 (s, 1 H), 5.12 (s, 1 H), 4.58 (td, J = 13.0, 4.8 Hz, 1 H), 3.42 (td, J = 13.0, 7.5 Hz, 1 H), 2.91 (dd, J = 7.5, 4.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 153.54, 144.42, 132.70, 131.56, 128.49, 127.12, 123.85, 123.51, 121.67, 117.77, 113.69, 59.07, 37.47, 22.94 ppm. HRMS (ESI): calcd. for $C_{16}H_{14}NO_2$ [M + H]$^+$ 252.1025; found 252.1019.

1,4-Dihydroxy-5,12b-dihydro-6*H*-isoindolo[1,2-*a*]isoquinolin-8-one (2b): By following the general procedure, imide **1b** (141 mg, 0.5 mmol) furnished the cyclized product **2b** (109 mg, 82% yield) as a colorless solid; m.p. 89 °C (dec). IR (KBr): $\tilde{\nu}$ = 3381, 1656, 1610, 1528 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.51 (s, 1 H), 8.81 (s, 1 H), 8.42–8.40 (m, 1 H), 7.69–7.67 (m, 1 H), 7.59–7.55 (m, 1 H), 7.49–7.45 (m, 1 H), 6.64 (d, J = 8.5 Hz, 1 H), 6.56 (d, J = 8.5 Hz, 1 H), 5.99 (s, 1 H), 4.44–4.40 (m, 1 H), 3.07–3.00 (m, 1 H), 2.80–2.77 (m, 1 H), 2.30–2.25 (m, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 168.30, 147.56, 147.48, 146.99, 132.09, 131.90, 128.30, 125.99, 122.94, 122.51, 121.90, 113.52, 113.21,

57.95, 37.89, 24.44 ppm. HRMS (ESI): calcd. for $C_{16}H_{14}NO_3$ [M + H]$^+$ 268.0974; found 268.0970.

4-Bromo-2-hydroxy-1-methoxy-5,12b-dihydro-6*H*-isoindolo[1,2-*a*]-isoquinolin-8-one (2d): By following the general procedure, imide **1d** (195 mg, 0.5 mmol) furnished the cyclized product **2d** (115 mg, 64% yield) as a colorless solid; m.p. 104 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3307, 1675, 1594, 1443 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33–8.31 (m, 1 H), 7.85–7.83 (m, 1 H), 7.52–7.48 (m, 1 H), 7.45–7.42 (m, 1 H), 7.02 (s, 1 H), 6.17 (s, 1 H), 6.07 (s, 1 H), 4.70 (ddd, J = 13.0, 5.3, 1.3 Hz, 1 H), 3.91 (s, 3 H), 3.08 (td, J = 13.0, 3.2 Hz, 1 H), 2.91–2.87 (m, 1 H), 2.72–2.64 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.54, 145.97, 145.26, 142.78, 132.49, 131.96, 128.45, 127.99, 125.78, 123.31, 122.64, 114.40, 113.81, 57.93, 56.42, 38.53, 30.92 ppm. HRMS (ESI): calcd. for $C_{17}H_{15}BrNO_3$ [M + H]$^+$ 360.0235; found 360.0235.

General Procedure for TfOH-Mediated Cyclization at 0 °C: An oven-dried two-neck round-bottom flask that had a septum in the side arm was cooled to room temperature under a steady stream of nitrogen. The flask was charged with a stir bar, the imide (0.5 mmol), and dry dichloromethane (15 mL), and the resulting solution was cooled to 0 °C (by using ice). To this solution was added TfOH (0.2 mL, 2 mmol) with stirring. After 30 min, the reaction mixture was quenched with water (10 mL) followed by $NaHCO_3$ (1 g). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2× 15 mL). The combined organic extracts were washed with brine solution, dried with anhydrous Na_2SO_4, and filtered. The solution was concentrated to dryness by using a rotary evaporator. The dried compound was purified by chromatography on a short silica gel column (ethyl acetate/hexane, 50:50).

2,12b-Dihydroxy-3-methoxy-5,12b-dihydro-6*H*-isoindolo[1,2-*a*]isoquinolin-8-one (2c): By following the general procedure, imide **1c** (148 mg, 0.5 mmol) furnished the cyclized product **2c** (123 mg, 83% yield) as a colorless solid; m.p. 183 °C. IR (KBr): $\tilde{\nu}$ = 3294, 2935, 2845, 1653, 1606, 1524, 1426, 1367, 1201, 1108, 1031, 761, 682 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.96 (s, 1 H), 7.97 (d, J = 7.6 Hz, 1 H), 7.68 (t, J = 7.6 Hz, 1 H), 7.64 (d, J = 7.4 Hz, 1 H), 7.51 (t, J = 7.4 Hz, 1 H), 7.34 (s, 1 H), 6.85 (s, 1 H), 6.66 (s, 1 H), 4.21–4.17 (m, 1 H), 3.71 (s, 3 H), 3.42–3.35 (m, 1 H), 2.77–2.67 (m, 2 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 165.86, 148.80, 147.50, 144.93, 132.25, 130.34, 129.25, 129.09, 125.04, 123.48, 122.43, 114.47, 111.80, 85.35, 55.50, 34.50, 28.29 ppm. HRMS (ESI): calcd. for $C_{17}H_{14}NO_3$ [M – OH] 280.0968; found 280.0970.

14b-Hydroxy-7,8-dihydrobenzo[*g*]isoindolo[1,2-*a*]isoquinolin-5-(14b*H*)-one (2e): By following the general procedure, imide **1e** (150 mg, 0.5 mmol) furnished the cyclized product **2e** (137 mg, 91% yield) as a colorless solid; m.p. 196 °C (dec). IR (KBr): $\tilde{\nu}$ = 3273, 2926, 2823, 1674, 1601, 1439, 1318, 1410, 1104, 1025 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.46 (s, 1 H), 8.34 (d, J = 7.7 Hz, 1 H), 8.01–7.99 (m, 1 H), 7.83–7.80 (m, 1 H), 7.77–7.73 (m, 2 H), 7.69 (d, J = 7.4 Hz, 1 H), 7.58–7.54 (m, 1 H), 7.51–7.46 (m, 2 H), 7.14 (s, 1 H), 4.19–4.13 (m, 1 H), 3.62–3.56 (m, 1 H), 3.24–3.17 (m, 1 H), 3.09–3.01 (m, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 166.00, 148.23, 135.99, 132.69, 132.46, 132.38, 131.62, 130.64, 129.38, 127.99, 126.94, 126.83, 126.66, 126.62, 125.70, 124.22, 122.55, 86.32, 35.25, 28.55 ppm. HRMS (ESI): calcd. for $C_{20}H_{15}NNaO_2$ [M + Na]$^+$ 324.1000; found 324.1001.

12b-Hydroxy-5,6-dihydrobenzo[*f*]isoindolo[1,2-*a*]isoquinolin-8-(12b*H*)-one (2f): By following the general procedure (but using ethyl acetate as the extracting solvent instead of dichloromethane), imide **1f** (150 mg, 0.5 mmol) furnished the cyclized product **2f** (131 mg, 87% yield) as a colorless solid; m.p. 160 °C (dec). IR (KBr): $\tilde{\nu}$ = 3281, 2936, 2830, 1661, 1614, 1435, 1326, 1414, 1116, 1029 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27 (d, J = 7.68 Hz, 1 H), 8.21 (d, J = 8.76 Hz, 1 H), 8.00 (d, J = 8.16 Hz, 1 H), 7.91–7.89 (m, 1 H), 7.86 (d, J = 8.76 Hz, 1 H), 7.71–7.66 (m, 2 H), 7.59–7.51 (m, 3 H), 7.20 (s, 1 H), 4.49–4.44 (m, 1 H), 3.61–3.54 (m, 1 H), 3.35–3.29 (m, 1 H), 3.13–3.04 (m, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 166.04, 148.58, 134.45, 132.47, 132.26, 131.26, 130.56, 130.21, 129.47, 128.21, 126.72, 126.60, 126.37, 125.53, 124.29, 124.01, 122.62, 85.74, 33.81, 25.62 ppm. HRMS (ESI): calcd. for $C_{20}H_{15}NNaO_2$ [M + Na]$^+$ 324.1000; found 324.1001.

12b-Hydroxy-2,3,11,12-tetramethoxy-5,12b-dihydro-6*H*-isoindolo-[1,2-*a*]isoquinolin-8-one (2ga): By following the general procedure, imide **1g** (186 mg, 0.5 mmol) furnished the crude product mixture, which was purified by silica gel column chromatography (ethyl acetate/hexane, 60:40) to give the cyclized product **2ga** (158 mg, 85% yield) as a colorless solid; m.p. 158–160 °C. IR (KBr): $\tilde{\nu}$ = 3241, 2996, 2936, 2836, 1680, 1614, 1494, 1334, 1135, 967 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 7.48 (d, J = 8.2 Hz, 1 H), 7.03 (d, J = 8.2 Hz, 1 H), 6.5 (s, 1 H), 4.22 (ddd, J = 13.0, 6.1, 2.0 Hz, 1 H), 4.12 (s, 3 H), 3.96 (s, 3 H), 3.91 (s, 3 H), 3.83 (s, 3 H), 3.66 (s, 1 H), 3.44 (ddd, J = 13.0, 11.8, 4.5 Hz, 1 H), 3.00–2.92 (m, 1 H), 2.70 (ddd, J = 16.0, 4.3, 1.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.56, 157.24, 148.97, 147.79, 144.67, 140.30, 128.73, 127.09, 124.35, 119.90, 113.46, 112.00, 111.03, 87.90, 61.91, 56.40, 55.97, 55.82, 34.74, 28.71 ppm. HRMS (ESI): calcd. for $C_{20}H_{21}NNaO_6$ [M + Na]$^+$ 394.1267; found 394.1266.

12b-Hydroxy-2,3,11-trimethoxy-5,12b-dihydro-6*H*-isoindolo[1,2-*a*]-isoquinolin-8-one (2ia): By following the general procedure, imide **1i** (170 mg, 0.5 mmol) furnished the cyclized product **2ia** (152 mg, 89% yield) as a colorless solid; m.p. 153–154 °C (dec). IR (KBr): $\tilde{\nu}$ = 3302, 2953, 2983, 1670, 1609, 1501, 1358, 1253 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.4 Hz, 1 H), 7.45 (d, J = 2.1 Hz, 1 H), 7.39 (s, 1 H), 6.98 (dd, J = 8.4, 2.1 Hz, 1 H), 6.58 (s, 1 H), 4.29 (ddd, J = 13.2, 5.9, 1.6 Hz, 1 H), 3.95 (s, 3 H), 3.91 (s, 3 H), 3.84 (s, 3 H), 3.45–3.38 (m, 1 H), 2.98–2.89 (m, 1 H), 2.69–2.65 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.40, 163.46, 150.35, 149.28, 147.90, 127.74, 127.63, 125.00, 123.05, 115.02, 111.41, 110.17, 108.76, 85.91, 56.15, 55.89, 55.77, 35.00, 28.95 ppm. HRMS (ESI): calcd. for $C_{19}H_{19}NNaO_5$ [M + Na]$^+$ 364.1161; found 364.1155.

Synthesis of 2ka and 2kb: By following the general procedure, imide **1k** (178 mg, 0.5 mmol) furnished the cyclized products **2ka** and **2kb** as a mixture (**2ka/2kb**, 62:38; 153 mg, 86% yield).

12b-Hydroxy-2,3-dimethoxy-12-nitro-5,12b-dihydro-6*H*-isoindolo-[1,2-*a*]-isoquinolin-8-one (2ka): M.p. 162–163 °C. IR (KBr): $\tilde{\nu}$ = 3393, 3074, 3021, 3158, 1672, 1610, 1573, 1512, 1451, 1315, 1301, 1255, 1127 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (dd, J = 8.1, 1.0 Hz, 1 H), 8.21 (dd, J = 7.4, 1.0 Hz, 1 H), 7.79 (dd, J = 8.1, 7.4 Hz, 1 H), 6.79 (s, 1 H), 6.43 (s, 1 H), 4.83 (s, 1 H), 3.92–3.89 (m, 2 H), 3.88 (s, 3 H), 3.68 (s, 3 H), 3.56–3.47 (m, 1 H), 3.0 (dt, J = 15.2, 5.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.82, 149.61, 147.00, 145.07, 139.06, 135.46, 131.44, 130.34, 128.94, 127.97, 127.71, 112.25, 108.42, 88.81, 56.04, 37.29, 26.89 ppm. HRMS (ESI): calcd. for $C_{18}H_{16}N_2NaO_6$ [M + Na]$^+$ 379.0906; found 379.0897.

12b-Hydroxy-2,3-dimethoxy-9-nitro-5,12b-dihydro-6*H*-isoindolo-[1,2-*a*]isoquinolin-8-one (2kb): M.p. 174–175 °C. IR (KBr): $\tilde{\nu}$ = 3346, 2989, 2925, 2812, 1667, 1608, 1548, 1483, 1336, 1130 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (dd, J = 5.7, 2.8 Hz, 1 H), 7.78–7.68 (m, 2 H), 7.35 (s, 1 H), 6.61 (s, 1 H), 4.45 (ddd, J = 13.1, 5.9, 1.4 Hz, 1 H), 3.95 (s, 3 H), 3.85 (s, 3 H), 3.53–3.46 (m, 1 H),

3.25 (s, 1 H), 3.06–2.98 (m, 1 H), 2.73 (dd, J = 16.3, 2.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.86, 150.24, 149.82, 148.16, 146.10, 133.35, 127.99, 126.76, 126.27, 124.06, 122.55, 111.59, 110.05, 85.44, 56.29, 55.95, 35.43, 28.79 ppm. HRMS (ESI): calcd. for $C_{18}H_{16}N_2NaO_6$ $[M + Na]^+$ 379.0906; found 379.0901.

Synthesis of 2la and 2lb: By following the general procedure above, imide **1l** (156 mg, 0.5 mmol) furnished the cyclized products **2la** and **2lb**.

12b-Hydroxy-2,3-dimethoxy-5,6-dihydropyrido[2′,3′:3,4]-pyrrolo-[2,1-*a*]isoquinolin-8(12b*H*)-one (2la): (75 mg, 48% yield), m.p. 173–174 °C. IR (KBr): $\tilde{\nu}$ = 3338, 2953, 2838, 1702, 1674, 1517, 1412, 1259, 1226, 1119, 1058 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (dt, J = 6.2, 2.8, 1.4 Hz, 1 H), 8.31 (dd, J = 7.8, 1.4 Hz, 1H), 7.44–7.47 (m, 1 H), 7.30 (s, 1 H), 4.67 (s, 1 H), 4.35–4.30 (m, 1 H), 3.93 (s, 3 H), 3.83 (s, 3 H) 3.53 (td, J = 16.8, 4.6, 3.9 Hz, 1 H), 2.75–2.71 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 151.4, 149.5, 148.6, 148.6, 148.0, 142.3, 131.4, 127.5, 126.7, 126.1, 111.5, 110.1, 84.5, 56.2, 55.9, 34.8, 29.0 ppm. HRMS (ESI): calcd. for $C_{17}H_{16}N_2NaO_4$ $[M + Na]^+$ 335.1008; 335.1001.

12b-Hydroxy-2,3-dimethoxy-5,6-dihydropyrido[3′,2′:3,4]-pyrrolo-[2,1-*a*]isoquinolin-8(12b*H*)-one (2lb): (72 mg, 46% yield), m.p. 128–130 °C. IR (KBr): $\tilde{\nu}$ = 3309, 3003, 2937, 2836, 1712, 1686, 1591, 1510, 1434, 1406, 1323, 1261, 1136, 1029 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.78 (dd, J = 4.9, 1.6 Hz, 1 H), 8.03 (dd, J = 7.6, 1.5 Hz, 1 H), 7.98 (s, 1 H), 7.40 (dd, J = 7.6, 4.9 Hz, 1 H), 4.47 (ddd, J = 13.2, 6.3, 1.4 Hz, 1 H), 3.94 (s, 3 H), 3.84 (s, 3 H) 3.60–3.52 (m, 1H), 3.04–2.96 (m, 1 H), 2.78 (dd, J = 16.3, 3.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 164.8, 152.9, 149.5, 147.9, 131.8, 127.0, 126.0, 124.5, 124.3, 111.0, 84.7, 56.1, 55.9, 34.3, 28.6 ppm. HRMS (ESI): calcd. for $C_{17}H_{16}N_2NaO_4$ $[M + Na]^+$ 335.1008; found 335.1012.

General Procedure for TfOH-Mediated Cyclization at 0 °C and Reduction at Room Temperature: An oven-dried two-neck round-bottom flask that had septum in the side arm was cooled to room temperature under a steady stream of nitrogen. The flask was charged with a stir bar, the imide (0.5 mmol), and dry dichloromethane (15 mL), and the resulting solution was cooled to 0 °C. To this solution was added TfOH (0.2 mL, 2 mmol) with stirring. After the stipulated time, the contents were warmed to room temperature, and $NaBH_4$ (2 mmol) was added followed by TFA (1 mL). The resulting solution was stirred until the color disappeared. (Additional $NaBH_4$ and TFA were used if the color persisted for a long time). The reaction mixture was evaporated to dryness under reduced pressure. The solid residue was dissolved in dichloromethane (20 mL), and the insoluble material was removed by filtration. The filtrate was dried with anhydrous Na_2SO_4 and filtered. The solvent was evaporated under vacuum, and the crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 50:50).

Synthesis of Nuevamine (2ha) and Isonuevamine (2hb): By following the general procedure, imide **1h** (71 mg, 0.2 mmol) with TfOH (0.1 mL, 1 mmol) furnished the cyclized products **2ha** and **2hb** as a mixture. The procedure was carried out at two temperatures: (1) at 0 °C for 30 min to deliver the cyclized products **2ha** and **2hb** (59 mg, 86% yield) and (2) at –78 °C for 36 h to deliver the cyclized products **2ha** and **2hb** (63 mg, 92% yield).

10,11-Dimethoxy-5,11b-dihydro-6*H*-1,3-dioxa-6a-aza-indeno[5,6-*c*]-fluoren-7-one (2ha): M.p. 190–192; ref.[18] m.p. 194–196 °C. IR (KBr): $\tilde{\nu}$ = 2970, 2940, 2841, 1688, 1620, 1446, 1408, 1273, 1220, 1035 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (dd, J = 8.2, 0.8 Hz, 1 H), 7.14 (d, J = 8.2 Hz, 1 H), 7.03 (s, 1 H), 6.64 (s, 1 H), 5.95 (d, J = 1.4 Hz, 1 H), 5.88 (d, J = 1.4 Hz, 1 H), 5.45 (s, 1 H), 4.34–4.28 (m, 1 H), 4.06 (s, 3 H), 3.89 (s, 3 H), 3.42–3.35 (m, 1 H), 3.01–2.93 (m, 1 H), 2.75 (dt, J = 15.7, 4.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.16, 152.79, 147.33, 146.78, 146.51, 137.67, 128.32, 127.88, 125.05, 118.42, 116.24, 109.06, 105.49, 101.08, 62.54, 68.01, 56.74, 38.29, 29.29 ppm.

8,9-Dimethoxy-5,11b-dihydro-6*H*-1,3-dioxa-6a-aza-indeno[5,6-*c*]-fluoren-7-one (2hb): M.p. 210–212 °C (dec); ref.[19] m.p. 212 °C. IR (KBr): $\tilde{\nu}$ = 2972, 2922, 2887, 2868, 1682, 1620, 1495, 1481, 1409, 1269, 1078, 1034, 924 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, J = 8.2 Hz, 1 H), 7.31 (s, 1 H), 7.07 (d, J = 8.2 Hz, 1 H), 6.66 (s, 1 H), 5.92 (d, J = 1.3 Hz, 1 H), 5.86 (d, J = 1.3 Hz, 1 H), 5.63 (s, 1 H), 4.07–4.01 (m, 1 H), 3.99 (s, 3 H), 3.97 (s, 3 H), 3.59–3.53 (m, 1 H), 3.05–2.98 (m, 1 H), 2.89–2.82 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.62, 155.48, 146.77, 146.43, 144.34, 136.14, 128.81, 128.40, 126.64, 119.76, 113.21, 108.43, 107.52, 100.95, 60.52, 58.37, 56.29, 38.78, 28.91 ppm.

1,3,11,12-Tetramethoxy-5,12b-dihydro-6*H*-isoindolo[1,2-*a*]isoquinolin-8-one (2jb): By following the general procedure, imide **1j** (185 mg, 0.5 mmol) furnished the cyclized product **2jb** (147 mg, 83% yield) as a colorless solid; m.p. 146–147 °C. IR (KBr): $\tilde{\nu}$ = 3342, 2987, 2921, 2858, 1667, 1601, 1498, 1362, 1154 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.4 Hz, 1 H), 7.04 (d, J = 8.4 Hz, 1 H), 6.41 (s, 1 H), 6.24 (s, 1 H), 5.82 (s, 1 H), 4.63 (dd, J = 12.0, 4.7 Hz, 1 H), 4.04 (s, 3 H), 3.97 (s, 3 H), 3.85 (s, 3 H), 3.75 (s, 1 H), 3.01 (t, J = 12.0 Hz, 1 H), 2.94–2.85 (m, 1 H), 2.58 (d, J = 15.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.92, 159.55, 158.28, 152.43, 146.86, 140.58, 137.86, 125.11, 120.42, 116.91, 116.14, 105.42, 97.31, 62.47, 57.07, 56.86, 55.49, 55.15, 38.76, 31.25 ppm. HRMS (ESI): calcd. for $C_{20}H_{22}NO_5$ $[M + H]^+$ 356.1498; found 356.1492.

General Procedure for TfOH-Assisted Cyclization (0 °C to Room Temperature) and Reduction (at Room Temperature) by Using $NaBH_4$/MeOH System – Synthesis of Pyrroloisoquinolinones, Benzoquinolizinones, and Oxa-benzoquinolizinone: An oven-dried two-neck round-bottomed flask that had septum in the side arm was cooled to room temperature under a steady stream of nitrogen. The flask was charged with a stir bar, the imide (0.5 mmol), and dry dichloromethane (15 mL), and the resulting solution was cooled to 0 °C. To this solution was added TfOH (0.2 mL, 2 mmol) with stirring. After the stipulated time, the contents were warmed to room temperature, and $NaBH_4$ (2 mmol) was added followed by methanol (2.5 mL). The solution was stirred until the color disappeared. (Additional $NaBH_4$ and MeOH were used if the color persisted for a long time). To this mixture was added acetone, and the solution was evaporated to dryness under reduced pressure. The solid residue was dissolved in dichloromethane (20 mL), and the insoluble material was removed by filtration. The filtrate was dried with anhydrous Na_2SO_4 and filtered. The solvent was evaporated under vacuum, and the crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 50:50).

8,9-Dimethoxy-1,2,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one (4a): By following the general procedure, imide **3a** (131 mg, 0.5 mmol) furnished the cyclized product **4a** (110 mg, 89% yield) as a colorless solid, m.p. 106–108 °C; ref.[20] m.p. 97–99 °C. IR (KBr): $\tilde{\nu}$ = 2934, 2835, 1708, 1609, 1519, 1420, 1250, 1115, 1006, 862, 764 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.61 (s, 1 H), 6.57 (s, 1 H), 4.72 (t, J = 8.0 Hz, 1 H), 4.32 (ddd, J = 12.7, 6.0, 2.0 Hz, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.05–2.98 (m, 1 H), 2.93–2.85 (m, 1 H), 2.70–2.44 (m, 4 H), 1.89–1.81 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.14, 148.19, 148.01, 129.40, 125.61,

111.79, 107.76, 56.57, 56.09, 55.94, 37.07, 31.77, 28.09, 27.76 ppm.

8,10-Dimethoxy-1,2,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-(10b*H*)-one (4b): By following the general procedure, imide **3b** (131 mg, 0.5 mmol) furnished the cyclized product **4b** (107 mg, 87% yield) as a colorless solid; m.p. 121–122 °C. IR (KBr): $\tilde{\nu}$ = 2974, 1689, 1586, 1442 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.33 (d, J = 2.4 Hz, 1 H), 6.24 (d, J = 2.4 Hz, 1 H), 4.75–4.71 (m, 1 H), 4.40–4.35 (m, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 2.87–2.78 (m, 3 H), 2.66–2.62 (m, 1 H), 2.53–2.47 (m, 1 H), 2.40–2.33 (m, 1 H), 1.69–1.60 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.49, 159.28, 157.70, 135.81, 118.60, 104.65, 96.93, 55.33, 55.21, 54.93, 36.63, 31.69, 29.70, 28.11 ppm. MS (LDI): calcd. for $C_{14}H_{17}NO_3$ $[M + H]^+$ 248.1287; found 248.1300.

8-Methoxy-1,2,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one (4c): By following the general procedure, imide **3c** (116 mg, 0.5 mmol) furnished the cyclized product **4c** (97 mg, 89% yield) as a colorless semisolid that changed to a pale yellow color; m.p. 121–122 °C. IR (KBr): $\tilde{\nu}$ = 2933, 1682, 1611, 1502, 1449 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.03 (d, J = 8.4 Hz, 1 H), 6.80 (dd, J = 8.4, 2.8 Hz, 1 H), 6.67 (d, J = 2.8 Hz, 1 H), 4.73 (t, J = 8.0 Hz, 1 H), 4.25 (ddd, J = 12.8, 6.0, 2.8 Hz, 1 H), 3.79 (s, 3 H), 3.09–3.02 (m, 1 H), 2.98–2.88 (m, 1 H), 2.77–2.72 (m, 1 H), 2.67–2.60 (m, 1 H), 2.59–2.52 (m, 1 H), 2.48–2.42 (m, 1 H), 1.88–1.79 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.51, 158.32, 134.88, 129.75, 125.86, 113.61, 113.17, 56.51, 55.30, 37.05, 31.78, 28.81, 27.66 ppm. MS (LDI): calcd. for $C_{13}H_{15}NO_2$ $[M + H]^+$ 218.1181; found 218.1183.

7,8-Dimethoxy-1,2,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one (4d): By following the general procedure, imide **3d** (131 mg, 0.5 mmol) furnished the cyclized product **4d** (80 mg, 65% yield) as a colorless solid; m.p. 121–122 °C. IR (KBr): $\tilde{\nu}$ = 2941, 2836, 1690, 1605, 1493, 1461, 1427, 1365, 1275, 1222, 1092, 1065, 1008, 811 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.84 (s, 1 H), 6.83 (s, 1 H), 4.71 (t, J = 7.9 Hz, 1 H), 4.30–4.25 (m, 1 H), 3.86 (s, 3 H), 3.80 (s, 3 H), 3.06–2.94 (m, 2 H), 2.80–2.74 (m, 1 H), 2.65–2.60 (m, 1 H), 2.58–2.52 (m, 1 H), 2.49–2.42 (m, 1 H), 1.89–1.79 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.21, 151.25, 146.49, 130.91, 128.28, 120.19, 111.12, 60.24, 56.31, 55.89, 36.67, 31.83, 27.69, 22.67 ppm. HRMS (ESI): calcd. for $C_{14}H_{17}NNaO_3$ $[M + Na]^+$ 270.1106; found 270.1107.

8,9,10-Trimethoxy-1,2,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-(10b*H*)-one (4e): By following the general procedure, imide **3e** (146 mg, 0.5 mmol) furnished the cyclized product **4e** (112 mg, 81% yield) as a colorless solid;[3g] m.p. 71–72 °C. IR (KBr): $\tilde{\nu}$ = 2938, 2838, 2361, 1689, 1602, 1494, 1459, 1417, 1355, 1313, 1276, 1121, 1096, 1039, 858 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.40 (s, 1 H), 4.78–4.74 (m, 1 H), 4.41–4.32 (m, 1 H), 3.93 (s, 3 H), 3.83 (s, 6 H), 2.88–2.80 (m, 3 H), 2.67–2.51 (m, 2 H), 2.41 (dd, J = 16.6, 9.5 Hz, 1 H), 1.75–1.65 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.42, 152.47, 150.68, 140.44, 129.38, 123.14, 107.44, 60.75, 60.47, 55.96, 55.04, 36.72, 31.74, 29.21, 28.51 ppm.

7,8,9-Trimethoxy-1,2,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-(10b*H*)-one (4f): By following the general procedure, imide **3f** (146 mg, 0.5 mmol) furnished the cyclized product **4f** (101 mg, 73% yield) as a colorless solid; m.p. 80–81 °C. IR (KBr): $\tilde{\nu}$ = 2944, 2831, 1686, 1602, 1458, 1364, 1310, 1268, 1106, 1026, 836, 639 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.39 (s, 1 H), 4.70 (t, J = 8.0 Hz, 1 H), 4.32 (ddd, J = 13.2, 6.4, 2.0 Hz, 1 H), 3.86 (s, 6 H), 3.85 (s, 3 H), 2.98–2.83 (m, 2 H), 2.69–2.44 (m, 4 H), 1.90–1.80 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.11, 152.65, 151.37, 141.09, 133.14, 120.25, 103.68, 60.99, 60.71, 60.39, 56.71, 56.63, 56.43, 56.25, 36.81, 31.91, 27.72, 22.39 ppm. HRMS (ESI): calcd. for $C_{15}H_{19}NNaO_4$ $[M + Na]^+$ 300.1212; found 300.1210.

8-Benzyloxy-9-methoxy-1,2,5,6-tetrahydropyrrolo[2,1-*a*]-isoquinolin-3(10b*H*)-one (4g): By following the general procedure, imide **3g** (170 mg, 0.5 mmol) furnished the crude product mixture, which was purified by silica gel column chromatography (ethyl acetate/hexane, 40:60) to give the cyclized product **4g** (74 mg, 46% yield) as a colorless solid; m.p. 185–187 °C. IR (KBr): $\tilde{\nu}$ = 2925, 2843, 1678, 1491, 1442, 1363, 1318, 1277, 1238, 1188, 1154, 1122, 1076, 943, 735, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.23 (m, 2 H), 7.18–7.15 (m, 1 H), 7.09–7.07 (m, 2 H), 6.58 (s, 1 H), 5.66 (s, 1 H), 4.79–4.75 (m, 1 H), 4.39–4.34 (m, 1 H), 4.11 (s, 2 H), 3.89 (s, 3 H), 2.90–2.85 (m, 1 H), 2.82–2.75 (m, 1 H), 2.64–2.60 (m, 1 H), 2.52–2.41 (m, 2 H), 2.36–2.28 (m, 1 H), 1.56–1.51 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.18, 145.07, 143.23, 139.65, 128.79, 128.39, 127.70, 125.93, 125.52, 122.47, 109.93, 56.52, 55.93, 37.04, 31.76, 31.53, 30.12, 29.33 ppm. HRMS (ESI): calcd. for $C_{20}H_{21}NNaO_3$ $[M + Na]^+$ 346.1419; found 346.1422.

9,11-Dimethoxy-2,3,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]-isoquinolin-4-(11b*H*)-one (6a): By following the general procedure, imide **5a** (139 mg, 0.5 mmol) furnished the cyclized product **6a** (110 mg, 84% yield) as a colorless solid; m.p. 124 °C. IR (KBr): $\tilde{\nu}$ = 2944, 1629, 1454, 1343 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.27 (d, J = 2.4 Hz, 1 H), 6.20 (d, J = 2.0 Hz, 1 H), 4.86 (ddd, J = 12.0, 4.4, 1.6 Hz, 1 H), 4.62 (dd, J = 10.8, 2.8 Hz, 1 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 2.80–2.72 (m, 1 H), 2.68–2.62 (m, 1 H), 2.56–2.45 (m, 3 H), 2.40–2.33 (m, 1 H), 1.80–1.74 (m, 2 H), 1.21–1.18 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.25, 159.03, 157.48, 137.99, 117.95, 104.54, 97.08, 55.31, 55.20, 54.23, 38.55, 31.80, 30.43, 29.71, 19.52 ppm. MS (LDI): calcd. for $C_{15}H_{19}NO_3$ $[M + H]^+$ 262.1443; found 262.1430.

9-Methoxy-2,3,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-4(11b*H*)-one (6b): By following the general procedure, imide **5b** (123 mg, 0.5 mmol) furnished the cyclized product **6b** (94 mg, 82% yield) as a colorless semisolid. IR (KBr): $\tilde{\nu}$ = 1685, 1609, 1461 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, J = 8.8 Hz, 1 H), 6.78 (dd, J = 8.8, 2.8 Hz, 1 H), 6.66 (d, J = 2.8 Hz, 1 H), 4.79–4.75 (m, 1 H), 4.61 (dd, J = 10.4, 4.8 Hz, 1 H), 3.81 (s, 3 H), 2.99–2.86 (m, 2 H), 2.73–2.69 (m, 1 H), 2.58–2.48 (m, 2 H), 2.41–2.32 (m, 1 H), 1.86–1.82 (m, 2 H), 1.73–1.63 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.61, 158.17, 136.42, 129.56, 125.96, 113.39, 112.79, 56.52, 55.27, 39.77, 32.18, 30.56, 29.16, 19.51 ppm. MS (LDI): calcd. for $C_{14}H_{17}NO_2$ $[M + H]^+$ 232.1338; found 232.1354.

9,10-Dimethoxy-2,3,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-4(11b*H*)-one (6c): By following the general procedure, imide **5c** (139 mg, 0.5 mmol) furnished the cyclized product **6c** (113 mg, 87% yield) as a colorless solid, m.p. 80–81 °C; ref.[20] m.p. 88–89 °C. IR (KBr): $\tilde{\nu}$ = 2943, 2838, 1683, 1619, 1516, 1459, 1358, 1268, 1220, 1024, 869 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.67 (s, 1 H), 6.62 (s, 1 H), 4.87 (ddd, J = 11.9, 4.3, 2.0 Hz, 1 H), 4.61 (dd, J = 10.6, 4.5 Hz, 1 H), 3.86 (s, 6 H), 2.94–2.77 (m, 2 H), 2.65–2.51 (m, 3 H), 2.42–2.33 (m, 1 H), 1.98–1.80 (m, 2 H), 1.72–1.62 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.61, 147.91, 147.79, 129.17, 127.34, 111.63, 108.32, 56.83, 56.21, 55.99, 39.83, 32.24, 31.02, 28.57, 19.65 ppm.

8,9-Dimethoxy-2,3,6,7-tetrahydro-1*H*-pyrido[2,1-*a*]isoquinolin-4-(11b*H*)-one (6d): By following the general procedure, imide **5d** (139 mg, 0.5 mmol) furnished the cyclized product **6d** (108 mg, 83% yield) as a colorless solid; m.p. 95–96 °C. IR (KBr): $\tilde{\nu}$ = 2952, 2833, 1693, 1493, 1464, 1417, 1331, 1276, 1223, 1080, 1046, 1003, 861, 634 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.91 (d, J = 8.6 Hz, 1 H), 6.81 (d, J = 8.6 Hz, 1 H), 4.84–4.80 (m, 1 H), 4.60

(dd, J = 10.4, 4.7 Hz, 1 H), 3.85 (s, 3 H), 3.79 (s, 3 H), 2.92–2.73 (m, 3 H), 2.56–2.48 (m, 2 H), 2.39–2.30 (m, 1 H), 1.97–1.77 (m, 2 H), 1.73–1.63 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.44, 151.11, 146.30, 130.88, 129.83, 120.42, 110.73, 60.41, 56.51, 55.95, 39.54, 32.40, 30.77, 23.15, 19.71 ppm. HRMS (ESI): calcd. for $C_{15}H_{19}NNaO_3$ $[M + Na]^+$ 284.1263; found 284.1261.

9,10-Dimethoxy-1,6,7,11b-tetrahydro-[1,4]oxazino[3,4-*a*]isoquinolin-4(3*H*)-one (6e): By following the general procedure, imide **5e** (140 mg, 0.5 mmol) furnished the crude product mixture, which was purified by silica gel column chromatography (ethyl acetate/hexane, 30:70) to give the cyclized product **6e** (53 mg, 40% yield) as a colorless solid; m.p. 120–122 °C. IR (KBr): $\tilde{\nu}$ = 3002, 2960, 2857, 2831, 1741, 1688, 1591, 1517, 1389, 1347, 1272, 1234, 1177, 1025, 967 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.65 (s, 1 H), 6.53 (s, 1 H), 4.93–4.88 (m, 2 H), 4.42 (dd, J = 8.0, 4.8 Hz, 1 H), 4.36 (d, J = 16.4 Hz, 1 H), 4.17 (d, J = 16.4 Hz, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.53–3.47 (m, 1 H), 2.96–2.88 (m, 1 H), 2.80 (td, J = 12.0, 3.2 Hz, 1 H), 2.66 (d, J = 16.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.06, 148.31, 147.94, 127.27, 123.20, 112.04, 107.74, 69.85, 67.98, 56.13, 55.90, 54.70, 38.05, 28.33 ppm. HRMS (ESI): calcd. for $C_{14}H_{17}NO_4$ $[M + H]^+$ 264.1236; found 264.1235.

9,11-Dimethoxy-6,7-dihydro-[1,4]oxazino[3,4-*a*]isoquinolin-4(3*H*)-one (6f′): By following the general procedure, imide **5f** (140 mg, 0.5 mmol) furnished the cyclized product **6f′** (97 mg, 74% yield) as a colorless solid; m.p. 121–123 °C. IR (KBr): $\tilde{\nu}$ = 2998, 2945, 2900, 2835, 1674, 1592, 1474, 1412, 1310, 1208, 1155, 1106, 971, 832, 734, 644 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (s, 1 H), 6.40 (s, 1 H), 6.32 (s, 1 H), 4.46 (s, 2 H), 3.83–3.81 (m, 8 H), 2.83 (t, J = 6.0 Hz, 2 H) ppm. ^{13}C NMR(100 MHz, $CDCl_3$): δ = 163.23, 159.10, 157.36, 136.66, 131.98, 116.41, 109.67, 104.91, 97.79, 67.20, 55.61, 55.50, 37.66, 30.25 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}NNaO_4$ $[M + Na]^+$ 284.0899; found 284.0899.

General Procedure for TfOH-Assisted Cyclization at Elevated Temperature (70 °C) and Reduction (at Room Temperature) by Using $NaBH_4$/MeOH System: An oven-dried two-neck round-bottom flask that had a septum in the side arm was cooled to room temperature under a steady stream of nitrogen. The flask was charged with a stir bar, the substrate (0.5 mmol), and TfOH (for equivalents, see Table 3), and the resulting mixture was stirred and heated at 70 °C. After the stipulated time, the contents were cooled to room temperature under nitrogen, and dry CH_2Cl_2 (10 mL) was added followed by the addition of $NaBH_4$ (2 mmol) and methanol (2.5 mL). The solution was stirred until the color disappeared. (Additional $NaBH_4$ and MeOH were used if the color persisted for a long time). To this mixture was added acetone, and the solution was concentrated to dryness under reduced pressure. The solid residue was dissolved in dichloromethane (20 mL), and the insoluble material was removed by filtration. The filtrate was dried with anhydrous Na_2SO_4 and filtered. The solvent was evaporated under vacuum, and the crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 50:50).

8-Methyl-1,2,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one (4h): By following the general procedure, imide **3h** (108 mg, 0.5 mmol) furnished the cyclized product **4h** (79 mg, 79% yield) as a colorless semisolid. IR (KBr): $\tilde{\nu}$ = 2930, 2847, 1682, 1429, 1364, 1307, 1171, 1035, 810, 659 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, J = 7.9 Hz, 1 H), 7.01 (d, J = 7.9 Hz, 1 H), 6.96 (s, 1 H), 4.74 (t, J = 7.9 Hz, 1 H), 4.25 (ddd, J = 12.8, 6.0, 2.6 Hz, 1 H), 3.09–3.01 (m, 1 H), 2.94–2.86 (m, 1 H), 2.76–2.70 (m, 1 H), 2.68–2.61 (m, 1 H), 2.59–2.52 (m, 1 H), 2.48–2.42 (m, 1 H), 2.31 (s, 3 H), 1.89–1.79 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.42, 136.69, 134.75, 133.56, 129.76, 127.75, 124.83, 56.80, 37.23, 31.95, 28.64, 27.75, 21.16 ppm. HRMS (ESI): calcd. for $C_{13}H_{15}NNaO$ $[M + Na]^+$ 224.1051; found 224.1049.

1,2,5,6-Tetrahydropyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one (4i): By following the general procedure, imide **3i** (101 mg, 0.5 mmol) furnished the cyclized product **4i** (67 mg, 72% yield) as a colorless semisolid.[3k] IR (KBr): $\tilde{\nu}$ = 2978, 2921, 2851, 1687, 1421, 1360, 1307, 1266, 1168, 755 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.18 (m, 2 H), 7.15–7.11 (m, 2 H), 4.78 (t, J = 8.0 Hz, 1 H), 4.27 (ddd, J = 12.8, 6.0, 2.8 Hz, 1 H), 3.11–3.04 (m, 1 H), 2.99–2.91 (m, 1 H), 2.81–2.75 (m, 1 H), 2.71–2.63 (m, 1 H), 2.60–2.54 (m, 1 H), 2.50–2.43 (m, 1 H), 1.93–1.83 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.22, 137.54, 133.58, 129.11, 126.88, 126.80, 124.80, 56.76, 37.04, 31.77, 28.53, 27.49 ppm.

8-Bromo-1,2,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one (4j): By following the general procedure, imide **3j** (141 mg, 0.5 mmol) furnished the cyclized product **4j** (101 mg, 76% yield) as a colorless solid; m.p. 91–92 °C. IR (KBr): $\tilde{\nu}$ = 2934, 2839, 1692, 1426, 1309, 1171, 1076, 1022, 964, 817, 654 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.2 Hz, 1 H), 7.30 (s, 1 H), 6.99 (d, J = 8.2 Hz, 1 H), 4.70 (t, J = 7.8 Hz, 1 H), 4.29–4.24 (m, 1 H), 3.03 (td, J = 11.6, 4.0 Hz, 1 H), 2.95–2.87 (m, 1 H), 2.77–2.62 (m, 2 H), 2.59–2.42 (m, 2 H), 1.83–1.78 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.16, 136.53, 135.89, 131.93, 129.97, 126.55, 120.63, 56.44, 36.71, 31.68, 28.35, 27.42 ppm. HRMS (ESI): calcd. for $C_{12}H_{12}NOBrNa$ $[M + Na]^+$ 288.0000; found 288.0000.

Synthesis of (±)-Crispine A (7): An oven-dried two-neck round-bottom flask that had a septum in the side arm was cooled to room temperature under a steady stream of nitrogen. The flask was charged with a stir bar, $LiAlH_4$ (4 mmol), and dry THF (10 mL), and the resulting mixture was cooled to 0 °C. To this mixture was added a solution of **4a** (124 mg, 0.5 mmol) in dry THF (10 mL) with stirring. The contents were heated at 60 °C for 6 h and cooled to room temperature, and then diethyl ether (20 mL) was added. The reaction was quenched by the careful addition of saturated sodium potassium tartrate. The mixture was stirred for an additional 1 h followed by the addition of anhydrous $MgSO_4$. The mixture was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure, and the resultant crude material was purified by chromatography on a silica gel column (chloroform/methanol, 95:5) to afford crispine A [8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (**7**), 74 mg, 63% yield] as a colorless solid, m.p. 85–86 °C; ref.[8] m.p. 87–89 °C. IR (KBr): $\tilde{\nu}$ = 2934, 2835, 1708, 1609, 1519, 1420, 1250, 1115, 1006, 862, 764 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60 (s, 1 H), 6.56 (s, 1 H), 3.845 (s, 3 H), 3.842 (s, 3 H), 3.46 (t, J = 8.4 Hz, 1 H), 3.17 (ddd, J = 10.8, 5.6, 2.8 Hz, 1 H), 3.09–2.97 (m, 2 H), 2.76–2.56 (m, 3 H), 2.36–2.28 (m, 1 H), 1.97–1.86 (m, 2 H), 1.77–1.67 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.41, 147.31, 130.70, 126.14, 111.36, 108.91, 62.83, 56.02, 55.91, 53.12, 48.26, 30.59, 27.90, 22.26 ppm.

Synthesis of Mixture of Trolline/Oleracein E (8): To a solution of **4a** (123 mg, 0.5 mmol) in dichloromethane (15 mL) was added BBr_3 (1 M in dichloromethane, 2 mL, 2.0 mmol) at –20 °C. After stirring for 5 h at –20 °C, the reaction mixture was quenched with MeOH (5.0 mL), and the solvent was evaporated under the reduced pressure. The MeOH addition and evaporation process was repeated (5×).[3h] The residue was washed with a small portion of MeOH (1 mL) to give a mixture of trolline and oleracein E [8,9-dihydroxy-1,2,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one (**8**), 90 mg, 82% yield] as a colorless solid, m.p. 253–254 °C; ref.[3h]

m.p. 252 °C. IR (KBr): ṽ = 3328, 3119, 2975, 2928, 2899, 1653, 1615, 1524, 1471, 1442, 1353, 1306, 1274, 1206, 1188, 1159, 1138, 870, 779, 656, 614 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 8.85 (s, 1 H), 8.80 (s, 1 H), 6.50 (s, 1 H), 6.49 (s, 1 H), 4.57 (t, J = 8.0 Hz, 1 H), 3.96 (ddd, J = 12.7, 5.4, 3.1 Hz, 1 H), 2.94–2.87 (m, 1 H), 2.59–2.51 (m, 3 H), 2.45–2.36 (m, 1 H), 2.25–2.18 (m, 1 H), 1.64–1.54 (m, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 171.97, 144.11, 143.95, 128.34, 123.64, 115.32, 111.60, 55.51, 36.57, 31.19, 27.32, 27.25 ppm.

Synthesis of (±)-Erythrinarbine (9): An oven-dried two-neck round-bottom flask that had a septum in the side arm was cooled to room temperature under a steady stream of nitrogen. The flask was charged with a stir bar, imide **3k** (1 mmol), and dry dichloromethane (15 mL), and the resulting mixture was cooled to 0 °C. To this solution was added TfOH (0.4 mL, 4 mmol) with stirring. The reaction was stirred for 3 h, and then $NaBH_4$ (4 mmol) was added followed by methanol (4 mL). The solution was stirred until the color disappeared. To this mixture was added acetone, and the solution was evaporated to dryness under reduced pressure. The solid residue was dissolved in dichloromethane (50 mL), and the insoluble material was removed by filtration. The filtrate was dried with anhydrous Na_2SO_4 and filtered. The solvent was evaporated under vacuum, and the crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 50:50) to afford (±)-erythrinarbine [8-methoxy-9-hydroxy-1,2,5,6-tetrahydropyrrolo-[2,1-*a*]isoquinolin-3(10b*H*)-one (**9**), 177 mg, 76% yield] as a colorless solid, m.p. 206–207 °C; ref.[13] m.p. 193–194 °C. IR (KBr): ṽ = 3113, 3020, 2986, 2844, 1670, 1585, 1511, 1465, 1446, 1360, 1298, 1264, 1220, 1118, 1030, 870 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.66 (s, 1 H), 6.59 (s, 1 H), 5.73 (s, 1 H), 4.67 (t, J = 7.6 Hz, 1 H), 4.27 (dd, J = 12.8, 4.4 Hz, 1 H), 3.86 (s, 3 H), 3.01 (td, J = 11.6, 4.0 Hz, 1 H), 2.90–2.82 (m, 1 H), 2.68–2.41 (m, 4 H), 1.82–1.78 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.42, 145.69, 144.80, 130.29, 124.97, 111.12, 110.75, 56.62, 56.12, 37.29, 31.94, 28.30, 27.80 ppm. HRMS (ESI): calcd. for $C_{13}H_{15}NNaO_3$ $[M + Na]^+$ 256.0950; found 256.0945.

CCDC-1028844 (for **2e**), -1028843 (for **2f**), -828127 (for **4a**), -1028840 (for **4b**), -877454 (for **4e**), -877455 (for **9**), -1028842 (for **2ia**), and -1028841 (for **2ka**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): ORTEP diagrams, preparations of the starting materials, and copies of ^1H and ^{13}C NMR spectra of all cyclized compounds.

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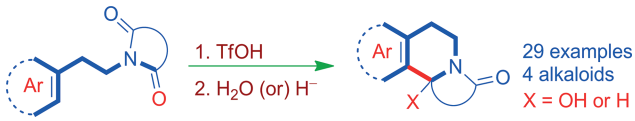
Alkaloid Synthesis



The isoquinoline-based polycyclic lactams and simple isoquinoline alkaloids were successfully assembled from the corresponding imides by using a TfOH-mediated (TfOH = trifluoromethanesulfonic acid) imide carbonyl activation and cyclization strategy. The regioselective cyclization of unsymmetrical phenethylimides with TfOH was studied by experimental and computational methods.

Keywords: Alkaloids / Nitrogen heterocycles / Lactams / Cyclization / Regioselectivity

