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Total Synthesis of (±)-Alantrypinone by Hetero Diels−Alder Reaction

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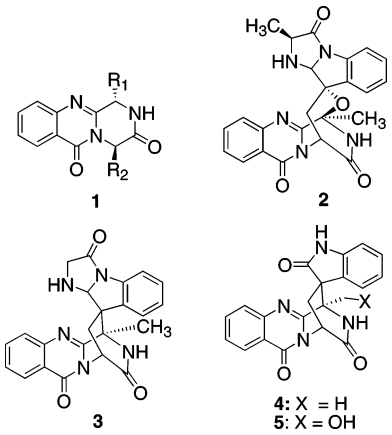
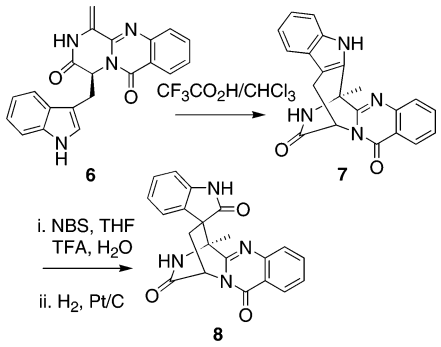
An efficient total synthesis of (±)-alantrypinone **4** by hetero Diels−Alder reaction of a novel pyrazine diene **9** with either a functionalized 3-alkylideneoxindole or 3-methyleneoxindole itself is described. The Diels−Alder reactions provide both the desired regiochemistry and exo selectivity. An interesting anionic equilibration between alantrypinone **4** and its epimer **31** or between its ester analogues **23** and **24** has been demonstrated, and a mechanism has been proposed.

Introduction

A number of polycyclic alkaloids biosynthetically derived from anthranilic acid and tryptophan have been the focus of total synthesis studies in the past decade. Such alkaloids have typically been isolated from diverse fungi of the genera *Penicillium* and *Aspergillus* and include glyantripine,[1] fiscalin B,[2] a series of fumiquinazolines designated A−I,[3] alantrypinone,[4] spiroquinazoline,[5] serantrypinone,[6] ardeemin,[7] and asperlicin.[8] Many of these compounds are built upon alkylated pyrazino [2,1-*b*]-quinazoline-3,6-dione (**1**) templates that have been synthesized by a variety of routes summarized by Söllhuber.[9] Of special structural complexity are those compounds, exemplified by fumiquinazoline C (**2**), spiroquinazoline (**3**), alantrypinone (**4**), and serantrypinone (**5**), in which the core pyrazino ring is bridged by a two- or three-atom bridge.



In the case of alantrypinone (**4**), Hart and Magomedov have met the synthetic challenge by designing a biomimetic solution.[10] The indole precursor **6** was subjected to a transannular iminium ion cyclization to form the bridged hexacyclic indole **7**. Subsequent NBS-mediated oxidative rearrangement of the bridging indole to the oxindole led to the spirocyclic structure of ent-alantrypinone **8**. Their synthesis was reported to proceed in 10 steps from isatoic anhydride in 12% overall yield.



Our own examination of the bicyclo[2,2,2]diazaoctane substructure of compounds **4** and **5** led us to consider the possibility that such structures might be constructed by a hetero Diels−Alder reaction of the hypothetical azadiene **9** with a 3-alkylideneoxindole (**10**) wherein Y could

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(10) (a) Hart, D. J.; Magomedov, N. A. *J. Am. Chem. Soc.* **2001**, *123*, 5892−5899. (b) Hart, D. J.; Magomedov, N. A. *Tetrahedron Lett.* **1999**, *40*, 5429−5432.

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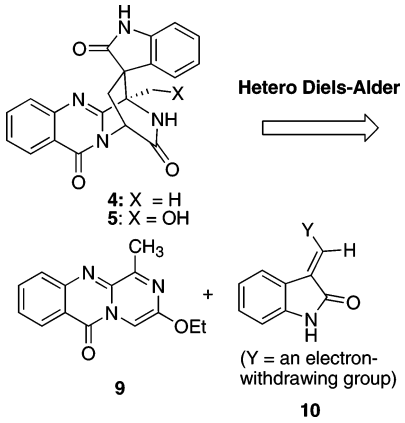
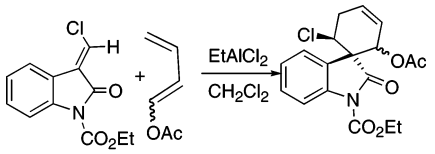
be an electron-withdrawing substituent such as CO_2R, SO_2Ph, or possibly hydrogen.



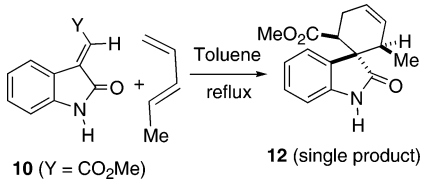
Although this strategy seemed to be rather direct, it faced several hazards. To our knowledge, the fully conjugated 6*H*-pyrazino[2,1-*b*]-quinazoline-6-one system exemplified by structure **9** had not been previously reported. Its stability was uncertain, and it was difficult to predict its behavior as a Diels−Alder diene. Moreover, the regiochemistry and the stereochemistry of its cycloaddition to an alkylideneoxindole of type **10** were unclear. We therefore analyzed the literature for relevant analogies to our proposed cycloaddition strategy.

Orientation in 3-Alkylideneoxindole Diels−Alder Reactions. The potential utility of 3-alkylideneoxindoles of type **10** in the synthesis of spirocyclic natural products has been recognized by several groups[11] and is elegantly exploited by Okada et al. in a total synthesis of the neurotoxic food poison neosurugatoxin.[12] Early work by Okada[13] and by Richards[14] clearly established that for the Diels−Alder addition of dienophiles such as **10** (in which Y is an electron-withdrawing group) with unsymmetrical dienes, the observed adduct regiochemistries are consistent with the lactam carbonyl as the regiodirecting control element in these additions. More recently, Gelmi et al. noted that the *N*-carboethoxy derivative of 3-chloromethyleneoxindole reacted with 1-acetoxy-1,3-butadiene (*E*/*Z* mixture) under Et_2AlCl catalyst to yield spirocyclic adducts (**11**) again consistent with the lactam as the regiodirecting element in the dienophile.[15] However, these workers noted that neither this dienophile nor its analogous 3-methylene compound reacted with 2-methyl- or 2,3-dimethyl-1,3-butadiene in the absence of Lewis acid catalyst, suggesting that a good electron-withdrawing group Y in the dienophile moiety was required for such thermal cycloadditions.

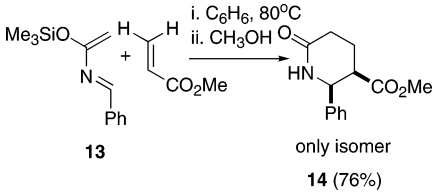
With the lactam carbonyl thus defined as the regiodirecting unit in the dienophile, the second question centers on exo vs endo stereochemistry. To obtain the correct isomer of alantrypinone (**4**), the hypothetical Diels−Alder addition of 3-alkylideneoxindole **10** to a diene such as **9**



must occur with an exo relationship between the lactam carbonyl and the diene π-system. In 1968, Richards and Ross reported that the dienophile **10** (Y = $COCH_3$) reacted with cyclopentadiene to give a 2:1 ratio of exo to endo adduct.[16] In 1992, Okada investigated this issue and reported essentially complete exo selectivity in the reaction of the dienophile **10** (Y = CO_2Me) with pure (*E*)- and (*Z*)-isomers of piperylene, as exemplified by the stereospecific formation of **12** below.[17]



Stereochemistry in 2-Azadiene Cycloadditions. Given the electron polarization anticipated for the azadiene **9**, the above examples seemed to predict favorable regiochemical outcome for its cycloaddition with dienophiles such as **10**. There is also specific literature regarding stereochemical issues in Diels−Alder additions to 2-azadienes. Ghosez has shown that both the uncatalyzed[18] and chiral Cu(II)-complex-catalyzed[19] Diels−Alder reaction of simple dienophiles with 3-siloxy-2-azadienes proceed with the desired regiochemistry for alantrypinone, and that the reaction is typically exo selective, as in **13** → **14** below. This group has also shown that cyclic 1,3-siloxy-2-aza-1,3-dienes likewise display strong exo selectivity.[20]



On the basis of the cited literature analogies, the stereochemical outcome anticipated for our Diels−Alder strategy seemed to be consistent with the stereochemical demands of the alantrypinone target structure. There remained the question of access to the desired diene system represented by structure **9**, as well as questions as to its intrinsic stability and its reactivity as a Diels−Alder diene.

Results and Discussion

1. Synthesis of the Azadiene 9 and Dienophiles. Given the apparent absence of the tricyclic 6*H*-pyrazino-

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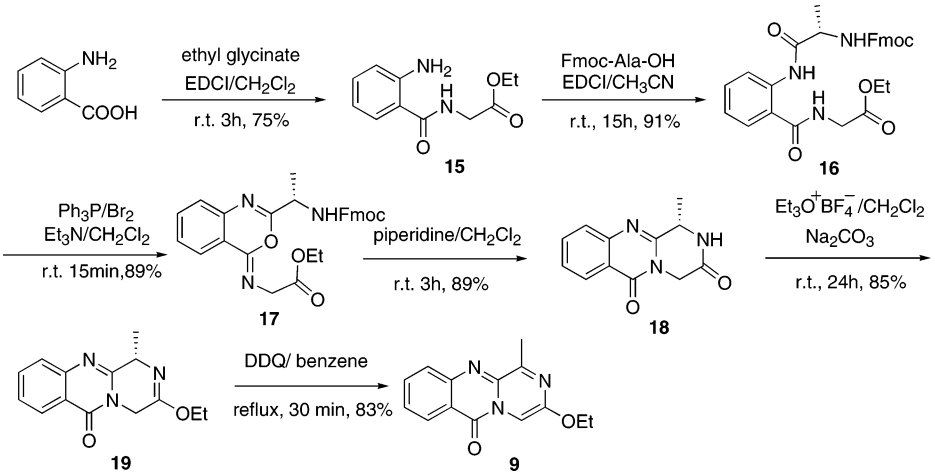
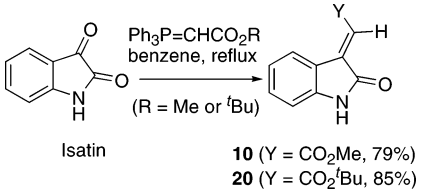
SCHEME 1



SCHEME 2



[2,1-*b*]-quinazolin-6-one system (e.g., **9**) in the literature, we undertook its synthesis from the closest accessible precursor, the parent 1-methyl-2,4-dihydro-1*H*-pyrazino-[2,1-*b*]quinazoline-3,6-dione (**18**) previously prepared by several groups.[9] In a slight modification of the Hernandez route, anthranilic acid was condensed with ethyl glycinate using EDCI to give the amide **15**, which was coupled with Fmoc-Ala-OH using EDCI in CH_3CN[21] to produce the protected diamide **16** in 68% overall yield. Reaction of the latter with Ph_3P and Br_2[21] led to the corresponding imino benzoxazine **17**, which was rearranged with piperidine to produce desired tricyclic dione **18** in 79% yield for the two steps.Dehydrogenation of the dione **18** to the requisite azadiene **9** followed the analogous chemistry of Blake et al.[22] Treatment of **18** with triethyloxonium fluoborate in the presence of sodium carbonate in CH_2Cl_2 was surpringly chemoselective to give 85% of the imino ether **19**. The latter was gently oxidized by DDQ in refluxing benzene to afford azadiene **9** as a stable, crystalline substance.

Dienophile **10** (Y = CO_2Me) was readily obtained in 79% yield by Wittig reaction of isatin with methyl (triphenylphosphoranylidene)acetate.[23] The (*E*)-stereochemistry of this ester had been previously established. Under the same conditions, dienophile **20** (Y = $CO_2{}^t$Bu) was produced in 85% yield, as shown in Scheme 2.

2. Synthesis of (±)-Alantrypinone from Diels−Alder Reaction Between 9 and 10 (Y = CO_2Me) or 20 (Y = $CO_2{}^t$Bu). The Diels−Alder reaction between dienophile **10** (Y = CO_2Me) with azadiene **9** proceeded smoothly in chloroform at room temperature to give both exo isomer **21** (66%) and endo isomer **22** (24%), as shown in Scheme 3.

This Diels−Alder reaction provided the desired regiochemistry and good exo selectivity. The regiochemistry of this Diels−Alder reaction was indicated by the presence in the ^{1}H NMR of **21** of a doublet (H-14) at δ 6.19 (J = 2.4 Hz) for the bridgehead proton and another doublet (H-15) at δ 3.54 (J = 2.4 Hz). The stereochemistry of **21** and **22** can be easily identified by ^{1}H NMR. The chemical shift of H-24 in the exo isomer **21** comes at δ 6.64, but in the endo isomer **22**, the chemical shift of H-24 comes at δ 5.77 because of the anisotropic shielding by the quinazoline π system. The above assignment is in agreement with the results of X-ray crystallography. Crystals suitable for single-crystal X-ray analysis of exo isomer **21** were obtained from methanol. The detailed X-ray data of **21** are shown in Supporting Information.

The effect of different solvents on the stereochemistry of this Diels−Alder reaction was studied, and the results are shown in Table 1. Chloroform seemed to be the best solvent for this hetero Diels−Alder reaction among those tested solvent systems.

Mild acid hydrolysis of exo adduct **21** and endo adduct **22** afforded **23** and **24**, respectively, in 95% yield. Cleavage of the methyl ester **23** with LiOH in MeOH or by nucleophilic attack with LiI in refluxing pyridine or DMF[24] failed to produce pure acid **25**. Such reactions provided product with the correct MS of the desired acid but which was shown to be a mixture by ^{1}H NMR.

Diels−Alder reaction of dienophile **20** (Y = $CO_2{}^t$Bu) and azadiene **9** proceeded successfully in chloroform at room temperature to give exo isomer **26** (65%) and endo isomer **27** (15%), as shown in Scheme 4. The chemical shift of H-24 in exo isomer **26** comes at δ 6.64, but the chemical shift of H-24 in endo isomer **27** comes at δ 5.74.

Mild acid hydrolysis of the exo isomer **26** afforded 97% of the *tert*-butyl ester **28**, which was converted to the desired acid **25** in quantitative yield by treatment with trifluoroacetic acid in CH_2Cl_2. Radical decarboxylation[25] of **25** by treating with *N*-hydroxypyridine-2-thione, DMAP,

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SCHEME 3

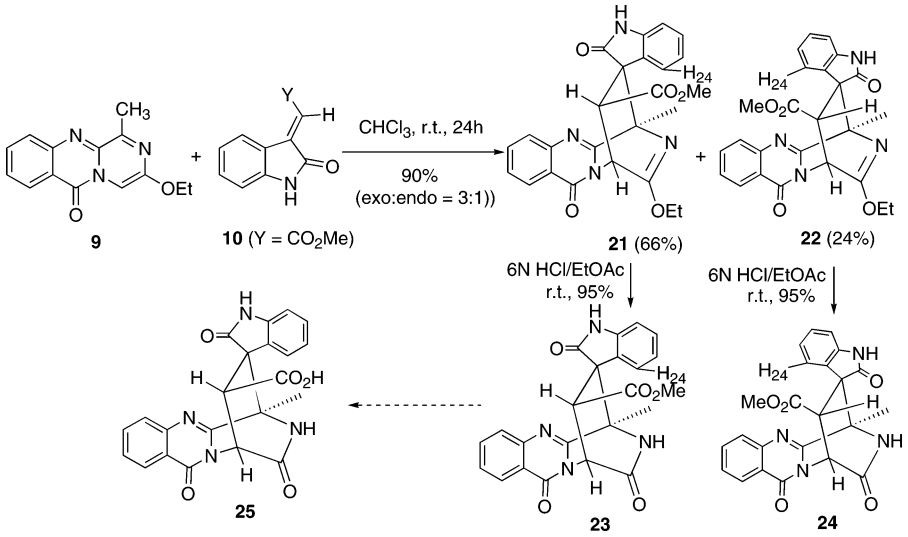

TABLE 1. Effect of Solvent on the Stereochemistry of the Diels–Alder Reaction between Azadiene 9 and Dienophile 10 (Y = CO_2Me)[a]

solvents	exo:endo[b]	solvents	exo:endo[b]
CH_3CN	1.85:1	C_6H_6–CH_2Cl_2 (1:1)	1.78:1
THF	1.61:1	EtOH–$CHCl_3$ (1:1)	1.27:1
CH_2Cl_2	2.91:1	$CHCl_3$	3.14:1
EtOAc	1.18:1		

[a] Diels–Alder reaction conditions: azadiene **9** (0.02 mmol), dienophile **10** (0.04 mmol), appropriate solvent (5 mL), rt, 24 h. [b] Ratio of exo:endo was measured by ^{1}H NMR spectroscopy.

and DCC to form the corresponding thiol ester, followed by reduction with tri-*n*-butyltin hydride and AIBN in refluxing toluene or by treating the acid chloride of **25** with the sodium salt of *N*-hydroxypyridine-2-thione, DMAP, and *tert*-butylthiol in refluxing toluene was not successful. Decarboxylation was finally achieved by conversion of the acid **25** to the corresponding phenylselenyl ester, followed by reduction with tri-*n*-butyltin hydride and AIBN[26] to give (±)-alantrypinone (**4**) in 66% yield. Our synthetic (±)-alantrypinone showed ^{1}H NMR and ^{13}C NMR spectra in agreement with the data reported in the literature.[4,]

3. Cycloaddition of Azadiene 9 with 3-Methyleneoxindole to Synthesize (±)-Alantrypinone.[27] Through a series of Diels–Alder reactions, we found that the new azadiene **9** was an active diene, which might be directly reacted with 3-methyleneoxindole. The synthesis of 3-methyleneoxindole was achieved according to the published route.[28] The aza Diels–Alder reaction between diene **9** and 3-methyleneoxindole proceeded readily in chloroform at room temperature to produce exo isomer **29** in 55% yield and endo isomer **30** in 18% yield, as shown in Scheme 5.

The regiochemistry of the Diels–Alder reaction was indicated by the presence in the ^{1}H NMR of a triplet near δ 6.1 for the bridgehead proton in each isomer, consistent with the presence of a vicinal CH_2 unit. Mild hydrolysis of adducts **29** and **30** provided (±)-alantrypinone (**4**) and (±)-17-epi-alantrypinone (**31**), respectively. The ^{1}H NMR of the 17-epimer displayed the diagnostic upfield signal of H-24 at δ 5.95, in contrast to that of alantrypinone at δ 7.16, as described in the literature.[10]

4. Anionic Rearrangement of Alantrypinone and Its Epimer. Although the stereochemical ratio of **29** to **30** in our Diels–Alder sequence thus favored the natural series, we envisioned the possibility that this ratio could be enhanced by thermal equilibration. When a dioxane or DMSO-d_6 solution of **30** was heated overnight to 100 °C, no conversion of **30** (endo) to **29** (exo) was observed. When a dioxane or DMSO-d_6 solution of **31** was heated overnight to 100 °C, no conversion to **4** was seen either. However, when **31** in DMSO-d_6 was treated with 0.1 equiv of DBU and held at 100 °C for 2.5 h, 75% of **31** was converted to **4**. Likewise, when (±)-alantrypinone (**4**) was heated for 2.5 h under the same conditions, a 3:1 ratio of **4** to **31** was again generated. This DBU-catalyzed equilibration did not occur at 100 °C in dioxane, and the reaction in DMSO-d_6 was not inhibited by the addition of excess *N*-phenylmaleimide. These data appear to exclude a retro Diels–Alder process for the equilibration. We conclude that this interesting epimerization is an intramolecular rearrangement involving an *anionic retro-Mannich reaction*, which probably proceeds by the mechanism described in Scheme 6.[29]

Similar epimerization occurred between esters **23** (exo) and **24** (endo). When a solution of **24** in DMSO-d_6 was heated at 100 °C for 12 h, no conversion to **23** was observed. When a solution of **23** in DMSO-d_6 was heated at 100 °C for 12 h, no conversion to **24** was seen either. However, when **24** in DMSO-d_6 was treated with DBU and heated at 100 °C for 12 h, **23** was produced as the major product, along with some other unidentified compounds. Likewise, when **23** was treated under the same condition, **24** was formed along with some other unidentified compounds, and most of **23** was unchanged.

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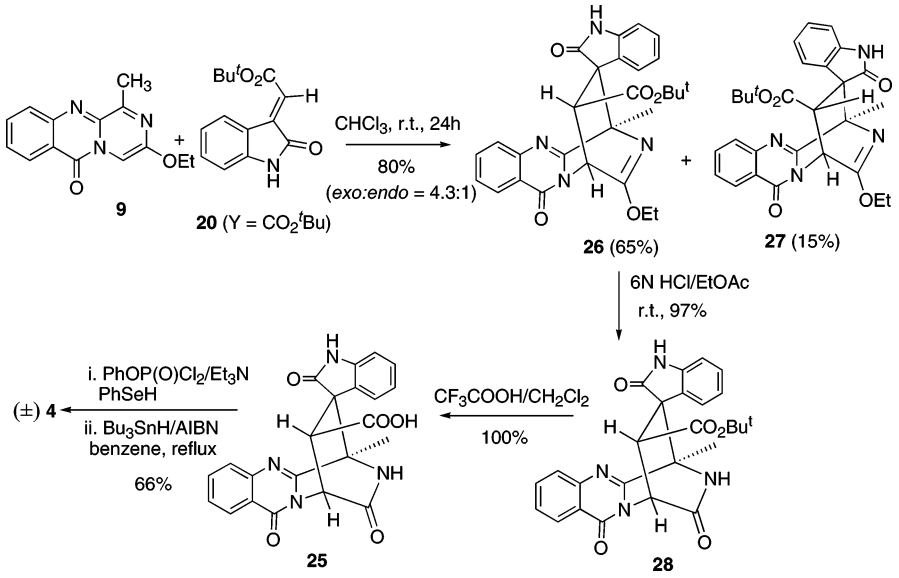
(28) Rossiter, S. *Tetrahedron Lett.* **2002**, *43*, 4671–4673.

(29) For a mechanistically related retroaldol epimerization in a synthesis of (±)-gelsemine, see: Atarashi, S.; Choi, J.-K.; Ha, D.-C.; Hart, D. J.; Kuzmich, D.; Lee, C.-S.; Ramesh, S.; Wu, S. C. *J. Am. Chem. Soc.* **1997**, *119*, 6226–6241. We thank Prof. N. Magomedov for directing us to this reference.

SCHEME 4



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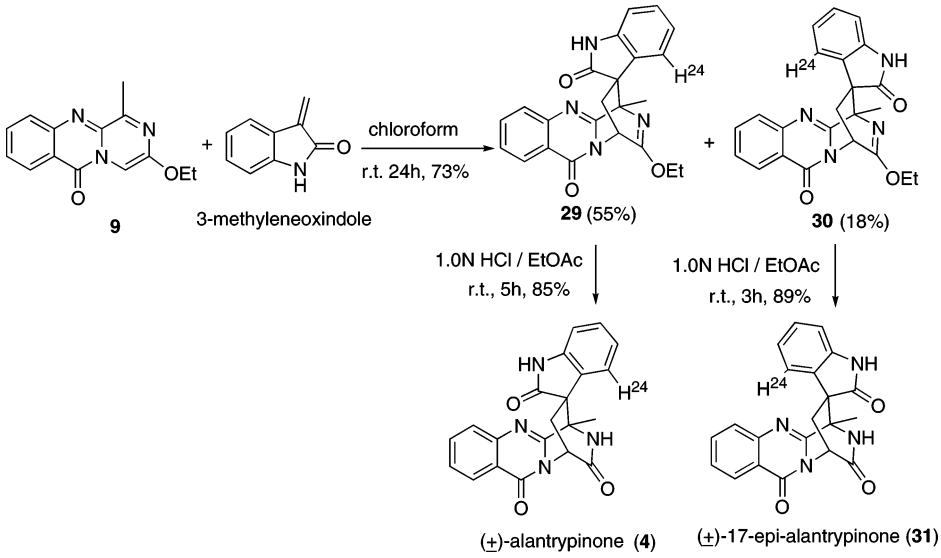
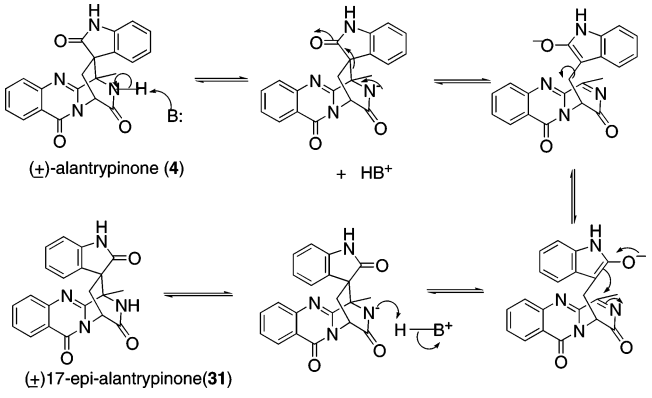


SCHEME 6



In conclusion, we have presented a concise total synthesis of (±)-alantrypinone by a hetero Diels−Alder reaction between either a functionalized 3-alkylideneoxindole or 3-methyleneoxindole itself with a novel fused pyrazine diene. The regiochemistry and exo selectivity of this Diels−Alder reaction was studied. This hetero Diels−Alder reaction provides an efficient method for the synthesis of (±)-alantrypinone and its analogues. The facile anionic equilibration between **4** and **31** has been demonstrated.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR were recorded in the solvent indicated at 400 and 100 MHz, respectively. Chemical shifts are expressed in parts per million downfield from TMS. Mass spectra were recorded by using APCI or API-ES mode. High-resolution mass analyses were carried out under the condition of DCI/NH_3, EI, or FAB as indicated. Flash chromatography was performed with 40−63 μm silica gel. TLC was performed on aluminum-precoated plates of silica gel 60 with an F_{254} indicator and visualized under UV light or developed by immersion in the solution of 20% phosphomolybdic acid in ethanol or in solution of 0.6% $KMnO_4$ and 6% K_2CO_3 in water.

3-Ethoxy-1-methyl-1,4-dihydro-2,4a,9-triaza-anthracen-10-one(19). To a solution of **18** (700 mg, 3.0 mmol) in 200 mL

of anhydrous dichloromethane was added anhydrous sodium carbonate(1.95 g, 18.0 mmol) and triethyloxonium fluoborate (870 mg, 4.5 mmol). The mixture was stirred at room temperature under argon for 24 h. The solid was filtered off, and the resulting filtrate was washed with saturated aqueous sodium carbonate solution (3 × 30 mL) and brine (2 × 20 mL) and dried over $MgSO_4$. Removal of the desiccant and evaporation of the solvent provided a gray solid residue, which was purified by flash column chromatography (hexanes/EtOAc, 1:1) to afford the desired product **19** (630 mg, 85%). Mp: 90−93 °C (EtOAc/hexanes). MS (API-ES, positive): 258 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, J = 7.1 Hz, 3H), 1.55 (d, J = 7.1 Hz, 3H), 4.01 (m, 1H), 4.20 (s, 2H), 4.53 (q, J = 7.0 Hz, 2H), 7.06 (ddd, J = 8.3, 7.8, 0.6 Hz, 1H), 7.31 (ddd, J = 8.3, 7.8, 1.4 Hz, 1H), 7.67(d, J = 8.2 Hz, 1H), 8.32 (dd, J = 7.9, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 22.0, 40.9, 56.7, 62.2, 121.0, 126.7, 127.1, 127.9, 134.6, 148.6,154.4, 159.4, 160.9. HRMS (DCI/NH_3): calcd for $C_{14}H_{16}N_3O_2$ [MH]$^+$ m/z 258.1243, found 258.1253.

Preparation of Azadiene 9. A solution of **18** (130 mg, 0.5 mmol) and DDQ (120 mg, 0.6 mmol) in 10 mL of benzene was refluxed under argon for 30 min. The reaction mixture was filtered, and the resulting mixture was filtered through basic alumina. The filtrate was evaporated under reduced pressure, and the residue was purified through flash column chromatography (hexanes/EtOAc, 4:1) to afford the desired product **9** (105 mg, 83%). Mp: 148−149 °C (EtOAc). MS (API-ES, positive): 256 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, J = 7.0 Hz, 3H), 2.73 (s, 3H), 3.75 (q, J = 7.0 Hz, 2H), 7.08 (ddd, J = 8.4, 7.8, 0.7 Hz, 1H), 7.33 (ddd, J = 8.4, 7.8, 1.4 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.88 (s, 1H), 8.54 (dd, J = 8.0, 0.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1, 22.1, 64.0, 97.0, 117.9, 126.8, 127.5, 128.1, 134.6, 139.6, 148.0,151.6, 158.1, 161.4. HRMS (DCI/NH_3): calcd for $C_{14}H_{14}N_3O_2$ [MH]$^+$ m/z 256.1086, found 256.1094.

Diels−Alder Reaction of Azadiene 9 with Dienophile 10. A solution of azadiene **9** (98 mg, 0.38 mmol) and dienophile **10** (156 mg, 0.77 mmol) in 10 mL of chloroform was stirred under argon for 24 h at room temperature. The solvent was removed under reduced pressure, and the residue was separated by flash chromatography (hexanes/EtOAc, 1:2) to afford exo adduct **21** (114 mg, 66%) as a white solid and endo adduct **22** (42 mg, 24%) as a white solid.

Compound 21. Mp: 199−200 °C (MeOH). MS (API-ES, positive): 459.1 (M + H). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.89 (s, 1H), 8.34 (d, J = 7.9 Hz, 1H), 7.76−7.73 (m, 2H), 7.53−7.49 (m, 1H), 7.17 (ddd, J = 8.8, 7.8, 1.3 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.96 (t, J = 7.4 Hz, 1H), 6.64 (d, J = 7.7 Hz, 1H), 6.19 (d, J = 2.4 Hz, 1H), 4.46−4.33 (m, 2H), 3.54 (d, J = 2.4 Hz, 1H), 3.14 (s, 3H), 1.52 (s, 3H), 1.47 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 17.1, 47.7, 51.7, 53.4, 57.3, 63.9, 66.5, 110.2, 120.0, 122.3, 125.0, 126.5, 126.8, 126.9, 127.9, 129.3, 134.4, 141.9, 147.3, 153.9, 159.1, 168.9, 172.4, 177.3. HRMS (FAB): calcd for $C_{25}H_{23}N_4O_5$ [MH]$^+$ m/z 459.1668, found 459.1678.

Compound 22. Mp: 217−218 °C (MeOH). MS (API-ES, positive): 459.1 (M + H). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.95 (s, 1H), 8.47 (d, J = 7.9 Hz, 1H), 7.79 (t, J = 7.2 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 6.91 (d, J = 7.7 Hz, 1H), 6.67 (t, J = 7.7 Hz, 1H), 6.26 (s, 1H), 5.77 (d, J = 7.6 Hz, 1H), 4.49−4.41 (m, 1H), 4.32−4.24 (m, 1H), 3.62 (s, 1H), 3.10 (s, 3H), 1.62 (s, 3H), 1.43 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 17.1, 48.7, 50.1, 51.9, 55.8, 64.1, 67.4, 109.7, 120.3, 122.2, 124.1, 126.1, 127.2, 127.3, 127.9, 129.3, 134.5, 141.3, 146.8, 153.3, 159.4, 168.5, 171.1, 177.1. HRMS (FAB): calcd for $C_{25}H_{23}N_4O_5$ [MH]$^+$ m/z 459.1668, found 459.1672.

Hydrolysis of 21. To a solution of **21** (26 mg, 0.057 mmol) in EtOAc (2 mL) was added an aqueous solution of 6 M HCl (0.1 mL). The reaction mixture was stirred for 12 h at room temperature and then extracted with EtOAc. The organic phase was washed with water and brine and then dried over Na_2SO_4. Evaporation of the solvent gave **23** (23 mg, 95%) as a white solid. Mp: >250 °C. MS (API-ES, positive): 431.0 (M + H). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.90 (s, 1H), 9.60 (s, 1H), 8.22 (dd, J = 8.0, 1.3 Hz, 1H), 7.89 (td, J = 8.4, 1.5 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.63 (dt, J = 7.9, 0.8 Hz, 1H), 7.36−7.32 (m, 1H), 7.09−7.04 (m, 2H), 6.96 (d, J = 7.7 Hz, 1H), 5.72 (t, J = 0.2 Hz, 1H), 3.54 (d, J = 0.2 Hz, 1H), 3.09 (s, 3H), 1.17 (s, 3H). HRMS (EI, 70 eV): calcd for $C_{23}H_{19}N_4O_5$ [MH]$^+$ m/z 431.1355, found 431.1366.

Hydrolysis of 22. To a solution of **22** (28 mg, 0.061 mmol) in EtOAc (2 mL) was added an aqueous solution of 6 M HCl (0.1 mL). The reaction mixture was stirred for 3 h at room temperature and then extracted with EtOAc. The organic phase was washed with water and brine and then dried over Na_2SO_4. Evaporation of the solvent gave **24** (25 mg, 95%) as a white solid. Mp: >250 °C. MS (API-ES, positive): 431.0 (M + H). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.01 (s, 1H), 9.43 (s, 1H), 8.29 (dd, J = 7.9, 0.9 Hz, 1H), 7.89 (ddd, J = 8.4, 7.1, 1.5 Hz, 1H), 7.69−7.64 (m, 2H), 7.18 (ddd, J = 7.9, 7.6, 0.8 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.60 (ddd, J = 8.2, 7.9, 0.7 Hz, 1H), 5.83 (d, J = 1.7 Hz, 1H), 5.52 (d, J = 7.6 Hz, 1H), 3.73 (d, J = 1.0 Hz, 1H), 2.93 (s, 3H), 1.24 (s, 3H).

Preparation of Dienophile 20. To a solution of isatin (1.0 g, 6.80 mmol) in dry benzene (40 mL) was added (*tert*-butoxycarbonylmethylene)triphenylphosphorane (2.43 g, 6.46 mmol). The resulting mixture was refluxed for 30 min. After cooling, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography (hexanes/EtOAc, 3:1 to 2:1) to afford **20** as an orange yellow solid. Mp: 122−123 °C (EtOAc). MS (API-ES, negative): 244.2 (M − H). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55 (d, J = 7.7 Hz, 1H), 7.33 (ddd, J = 7.7, 7.6, 0.9 Hz, 1H), 7.08 (ddd, J = 8.3, 8.0, 0.8 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.85 (s, 1H), 1.59 (s, 9H). HRMS (EI, 70 eV): calcd for $C_{14}H_{16}NO_3$ [MH]$^+$ m/z 246.1130, found 246.1130.

Diels−Alder Reaction of Azadiene 9 with Dienophile 20. A solution of azadiene **9** (67 mg, 0.26 mmol) and dienophile **20** (192 mg, 0.78 mmol) in 5 mL of chloroform was stirred under argon for 14 h at room temperature. The solvent was removed under reduced pressure, and the residue was separated by flash chromatograghy (hexanes/EtOAc, 3:1 to 1:1) to afford exo adduct **26** (85 mg, 65%) as a white solid and endo adduct **27** (20 mg, 15%) as a white solid.

Compound 26. Mp: 166 °C (dec) MS (API-ES, positive): 501.1 (M + H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.21 (s, 1H), 8.34 (d, J = 7.9 Hz, 1H), 7.77−7.71 (m, 2H), 7.52−7.48 (m, 1H), 7.16 (ddd, J = 8.0, 7.6, 0.8 Hz, 1H), 7.09 (d, J = 7.4 Hz, 1H), 6.94 (dd, J = 7.8 Hz, 7.5 Hz, 1H), 6.64 (d, J = 7.7 Hz, 1H), 6.16 (d, J = 2.3 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 3.43 (d, J = 2.3 Hz, 1H), 1.48 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H), 0.97 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 17.0, 27.4 (3C), 47.9, 54.3, 57.6, 63.9, 66.5, 82.6, 109.9, 120.1, 122.5, 126.3, 126.6, 126.8, 126.9, 127.9, 129.2, 134.3, 142.2, 147.4, 153.9, 159.1, 167.3, 172.5, 177.7. HRMS (FAB): calcd for $C_{28}H_{29}N_4O_5$ [MH]$^+$ m/z 501.2138, found 501.2129.

Compound 27. MS (API-ES, positive): 501.1 (M + H). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.70 (s, 1H), 8.45 (dd, J = 8.0, 1.2 Hz, 1H), 7.77 (ddd, J = 8.3, 7.2, 1.5 hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.55 (ddd, J = 8.1, 8.0, 1.1 Hz, 1H), 7.16 (ddd, J = 8.1, 7.9, 0.8 Hz, 1H), 6.90 (d, J = 7.7 hz, 1H), 6.63 (ddd, J = 8.1, 7.9, 0.6 Hz, 1H), 6.27 (d, J = 1.0 Hz, 1H), 5.74 (d, J = 7.6 Hz, 1H), 4.45−4.38 (m, 1H), 4.29−4.09 (m, 1H), 3.52 (d, J = 1.0 Hz, 1H), 1.58 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H), 0.89 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 16.9, 27.3 (3C), 48.9, 50.8, 55.9, 63.9, 67.5, 82.3, 109.5, 120.4, 122.4, 124.9, 126.2, 127.1, 127.3, 127.9, 129.2, 134.5, 141.8, 146.8, 153.7, 159.4, 166.7, 171.7, 177.5. HRMS (FAB): calcd for $C_{28}H_{29}N_4O_5$ [MH]$^+$ m/z 501.2138, found 501.2131.

Hydrolysis of 26. To a solution of **26** (60 mg, 0.12 mmol) in EtOAc (3 mL) was added an aqueous solution of 6 M HCl (0.3 mL). The reaction mixture was stirred for 18 h at room temperature and then extracted with EtOAc. The organic

phase was washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent gave **28** (55 mg, 97%) as a white solid. Mp: >250 °C. MS (API-ES, positive): 473.1 (M + H). ^{1}H NMR (CD_3OD, 400 MHz): δ 8.31 (dd, J = 8.0, 1.3 Hz, 1H), 7.88 (ddd, J = 8.5, 7.5, 1.5 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.62 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 7.42 (ddd, J = 7.9, 7.8, 1.3 Hz, 1H), 7.30 (d, J = 7.1 Hz, 1H), 7.12 (ddd, J = 7.8, 7.5, 1.1, 1H), 7.05 (d, J = 7.8 Hz, 1H), 5.91 (d, J = 2.4 Hz, 1H), 3.52 (d, J = 2.4 Hz, 1H), 1.35 (s, 3H), 1.04 (s, 9H). HRMS (FAB): calcd for $C_{26}H_{25}N_4O_5$ $[MH]^+$ m/z 473.1825, found 473.1836.

Preparation of Acid 25. To a suspension of **28** (55 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (2 mL). The resulting mixture was stirred at room temperature for 19 h. The solvent was evaporated under reduced pressure, and the residue was treated with 10 mL of dry toluene. The solvent was removed under reduced pressure to give the desired acid **25** (48 mg, 100%) as a white solid. Mp: >250 °C. MS (API-ES, positive): 417.0 (M + H). ^{1}H NMR (CD_3OD, 400 MHz): δ 8.32 (dd, J = 8.0, 1.3 Hz, 1H), 7.89 (ddd, J = 8.4, 7.2, 1.5 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.63 (ddd, J = 8.2, 8.0, 1.0, 1H), 7.39 (ddd, J = 7.8, 7.7, 1.2 Hz, 1H), 7.32 (d, J = 7.3 Hz, 1H), 7.10 (ddd, J = 8.0, 7.6, 0.8 Hz,1H), 7.01 (d, J = 7.7 Hz, 1H), 5.94 (d, J = 2.5 Hz, 1H), 3.58 (d, J = 2.5 Hz, 1H), 1.36 (s, 3H). HRMS (EI, 70 eV): calcd for $C_{22}H_{17}N_4O_5$ $[MH]^+$ m/z 417.1199, found 417.1182.

Synthesis of (±)-Alantrypinone (4) by Reductive Radical Decarboxylation of Acid 25. To a stirred solution of acid **25** (48 mg, 0.12 mmol) in THF (3 mL) were added triethylamine (50 μL, 0.36 mmol) and phenyldichlorophosphate (36 μL, 0.24 mmol) at 0 °C. After 30 min, triethylamine (84 μL, 0.60 mmol) was added, followed by addition of selenophenol (51 μL, 0.48 mmol). The reaction mixture was stirred at 0 °C for 10 min and then allowed to warm to room temperature. The mixture was diluted with EtOAc (30 mL), washed with water, 0.1 M HCl, and brine, and then dried over Na_2SO_4. The solvent was removed to afford the crude corresponding seleno ester as a white solid (50 mg). MS (API-ES, positive): 557.0 (M + H); calcd for $C_{28}H_{20}N_4O_4Se$, 556.0650.

The above crude seleno ester without purification was added to a refluxing solution of tri-*n*-butyltin hydride (262 mg, 0.90 mmol) and AIBN (5−10 mg) in benzene (5 mL). The reaction mixture was refluxed for 3 h. After cooling, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography to give the desired product **4** (29 mg, 66%) as a white solid. Mp: >300 °C. MS (API-ES, negative): 372 (M). ^{1}H NMR (400 MHz, CD_3OD): δ 1.22 (s, 3H), 2.49 (dd, J = 14.4, 2.1 Hz, 1H), 2.60 (dd, J = 14.4, 3.6 Hz, 1H), 5.81 (dd, J = 3.4, 2.1 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 7.16 (ddd, J = 8.2, 7.5, 0.7 Hz 1H), 7.30 (d, J = 7.0 Hz, 1H), 7.36 (ddd, J = 8.2, 7.7, 0.9 Hz, 1H), 7.60 (ddd, J = 8.8, 8.2, 1.0 Hz,1H), 7.76 (d, J = 8.0 Hz, 1H), 7.86 (ddd, J = 8.5, 7.8, 1.5 Hz, 1H), 8.29 (dd, J = 8.1, 1.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.3, 35.9, 51.9, 54.6, 61.7, 109.9, 120.0, 122.2, 123.7, 126.3, 127.1, 127.6, 129.0, 129.8, 134.6, 142.6, 146.8, 152.9, 158.2, 169.6, 176.5. HRMS (FAB): calcd for $C_{21}H_{17}N_4O_3$ $[MH]^+$ m/z 373.1311, found 373.1301.

Diels−Alder Reaction of 9 with 3-Methyleneoxindole. A solution of the aza-diene **9** (50 mg. 0.2 mmol) and 3-methyleneoxindole (145 mg, 1.0 mmol) in 10 mL of chloroform was stirred under argon for 24 h. The solvent was evaporated, and the residue was separated by flash column chromatography on silica gel (hexanes/ EtOAc, 1:1) to afford exo adduct **29** (44 mg, 55%) as a foam and endo adduct **30** (14 mg, 7.5%) as a white powder.

Compound 29. Mp: 223−225 °C (hexanes/EtOAc). MS-(API-ES, positive): 401 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (t, J = 7.0 Hz, 3H), 1.57 (s, 3H), 2.27 (dd, J_1 = 2.2 Hz, J_2 = 13.4 Hz, 1H), 2.59 (dd, J_1 = 2.8 Hz, J_2 = 13.7 Hz, 1H), 4.33−4.39 (m, 2H), 6.07 (dd, J_1 = 2.4 Hz, J_2 = 2.8 Hz, 1H), 6.81 (d, J = 7.7 Hz, 1H), 7.01−7.11 (m, 2H), 7.23−7.27 (m, 1H), 7.50−7.52 (m, 2H), 7.71−7.76 (m, 2H), 8.34 (d, J = 7.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 17.0, 37.8, 47.8, 54.9, 63.9, 67.1, 110.3, 120.4, 122.9, 124.3, 126.8, 126.9, 128.1, 129.1, 130.9, 134.4, 141.7, 147.7, 154.4, 159.6, 172.9, 178.8. HRMS (DCI/NH_3): calcd for $C_{23}H_{21}N_4O_2$ $[MH]^+$ m/z 401.1614, found 401.1599.

Compound 30. Mp 250−255 °C (dec). MS (API-ES, positive): 401 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (t, J = 7.1 Hz, 3H), 1.62 (s, 3H), 2.27 (dd, J = 13.7, 3.3 Hz, 1H), 2.60 (dd, J = 13.7, 1.9 Hz, 1H), 4.27−4.33 (m, H), 4.43−4.71 (m, 1H), 5.87 (d, J = 7.6 Hz, 1H), 6.09 (t, J = 2.1 Hz, 1H), 6.74 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 7.58 (t, J = 7.9 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.80 (ddd, J = 8.3, 7.9, 1.3 Hz, 1H), 8.16 (s, 1H), 8.41 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 17.2, 37.4, 48.3, 53.4, 64.1, 67.4, 109.8, 120.4, 123.0, 123.5, 127.1, 127.4, 128.4, 129.1, 130.4, 134.9, 141.3, 147.4,154.0, 159.4, 171.7, 178.6. HRMS (DCI/NH_3): calcd for $C_{23}H_{21}N_4O_2$ $[MH]^+$ m/z 401.1614, found 401.1619.

(±)-17-epi-Alantrypinone (31). To a solution of **30** (19 mg, 0.05 mmol) in 2 mL of EtOAc was added 0.5 mL of 1.0 N HCl. The mixture was stirred at room temperature for 3 h. The resulting mixture was extracted with 10 mL of EtOAc, and the organic layer was washed with water and brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to provide the desired product **31** as a white solid (15 mg, 89%). Mp: >300 °C. MS (API-ES, negative): 372 (M). ^{1}H NMR (400 MHz, THF-d_8): δ 1.35 (s, 3H), 2.29 (dd, J = 14.1, 3.9 Hz, 1H), 2.66 (dd, J = 14.1, 1.8 Hz, 1H), 5.67 (dd, J = 3.8, 1.9 Hz, 1H), 5.95 (d, J = 7.5 Hz, 1H), 6.63 (ddd, J = 8.2, 7.6, 0.8 Hz, 1H), 6.82 (d, J = 7.7 Hz, 1H), 7.10 (ddd, J = 8.5, 7.6, 1.0 Hz, 1H), 7.53 (ddd, J = 8.0, 7.2, 1.0 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.77 (ddd, J = 7.4, 1.7 Hz, 1H), 8.31 (dd, J = 7.9, 1.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.3, 35.1, 52.1, 52.5, 61.9, 109.5, 120.1, 121.5, 123.3, 126.5, 127.6, 127.7, 128.8, 129.2, 134.9, 142.3, 146.3, 152.4, 158.1, 168.8, 177.1. HRMS (FAB): calcd for $C_{21}H_{17}N_4O_3$ $[MH]^+$ m/z 373.1311, found 373.1301.

Synthesis of (±)-Alantrypinone (4) by Hydrolysis of 29. To a solution of **29** (40 mg, 0.1 mmol) in 2 mL of ethyl acetate was added 0.5 mL of 1.0 N HCl. The mixture was stirred at room temperature for 5 h. A precipitate was formed during the reaction. The resulting precipitate was collected by filtration to afford the desired product **4** as a white solid (32 mg, 85%). Mp: >300 °C. MS (API-ES, negative): 372 (M). ^{1}H NMR (400 MHz, CD_3OD): δ 1.22 (s, 3H), 2.49 (dd, J = 14.4, 2.1 Hz, 1H), 2.60 (dd, J = 14.4, 3.6 Hz, 1H), 5.81 (dd, J = 3.4, 2.1 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 7.16 (ddd, J = 8.2, 7.5, 0.7 Hz 1H), 7.30 (d, J = 7.0 Hz, 1H), 7.36 (ddd, J = 8.2, 7.7, 0.9 Hz, 1H), 7.60 (ddd, J = 8.8, 8.2, 1.0 Hz,1H), 7.76 (d, J = 8.0 Hz, 1H), 7.86 (ddd, J = 8.5, 7.8, 1.5 Hz, 1H), 8.29 (dd, J = 8.1, 1.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.3, 35.9, 51.9, 54.6, 61.7, 109.9, 120.0, 122.2, 123.7, 126.3, 127.1, 127.6, 129.0, 129.8, 134.6, 142.6, 146.8, 152.9, 158.2, 169.6, 176.5. HRMS (FAB): calcd for $C_{21}H_{17}N_4O_3$ $[MH]^+$ m/z 373.1311, found 373.1301.

Equilibration Experiment of 31 with 4. A solution of **31** (10 mg, 0.03 mmol) in DMSO-d_6 (0.5 mL) was placed in an NMR tube. The sealed tube was held in an oil bath at 100 °C for 12 h. At this point, ^{1}H NMR showed that no change of **31** took place.

DBU (0.5 mg, 0.1 equiv) was added to the above solution, which was held at 100 °C for 2.5 h. During this time, the color of the solution changed from colorless to dark. It was checked by ^{1}H NMR again. ^{1}H NMR showed that a mixture of **4** and **31** (3:1) had formed at this time.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **4**, **9**, and **19**−**31** and X-ray crystallographic data for compound **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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