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A Concise Total Synthesis of (±)-Alantrypinone by a Novel Hetero-Diels–Alder Reaction

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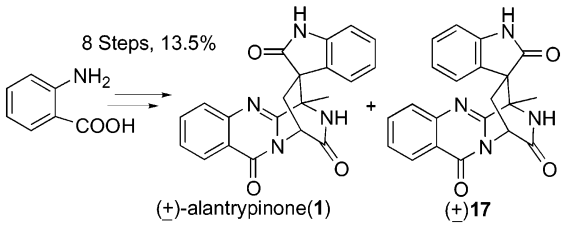
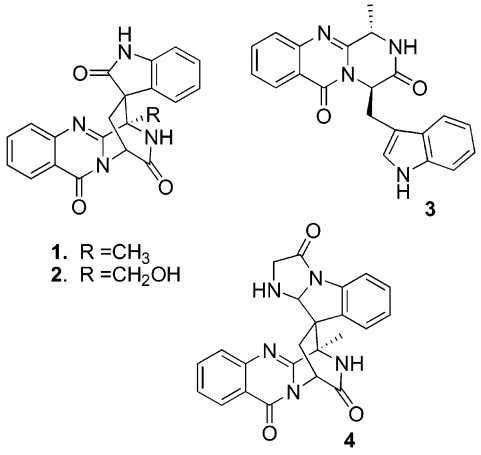
ABSTRACT



An efficient total synthesis of (±)-alantrypinone (1) and its 17-epi isomer (17) has been accomplished employing a novel aza-Diels–Alder reaction as the key step. The reaction sequence comprises 8 steps starting from anthranilic acid and proceeds in 13.5% overall yield. An interesting anionic equilibration between 1 and its epimer 17 has also been discovered.

In 1998 Larsen et al. reported the first isolation and structure elucidation of a hexacyclic alkaloid, (+)-alantrypinone (**1**), from extracts of the fungus *Penicillium thymicola.*[1] Three years later, the same group described a second, minor metabolite from this species, identified as the hydroxy derivative (−)-serantrypinone (**2**).[2] From the absolute configuration of **1** as determined by X-ray crystallography it was suggested that the alantrypinone molecule formally incorporates D-tryptophan and L-alanine, as seems to be the case for its congener, the known alkaloid fumiquinazoline F (**3**).[3]

Both (+)-alantrypinone (**1**) and (−)-serantrypinone (**2**) possess a tricyclic pyrazinoquinazolinedione base bridged by a 3-methyleneoxindole substructure. The unusual molecular architecture of these new compounds, and the claimed biological activity of the related spiroquinazoline structure **4**,[4] has led to speculation about their biosynthesis and to efforts toward their total synthesis. In particular, Hart and Magomedov[5] have recently reported a total synthesis of *ent*-alantrypinone (**7**) in 10 steps from isatoic anhydride in 12%



(1) Larsen, T. O.; Frydenvang, K.; Frisvad, J. C.; Christophersen, C. *J. Nat. Prod.* **1998**, *61*, 1154−1157.

(2) Ariza, M. R.; Larsen, T. O.; Petersen, B. O.; Duus, J. Q.; Christophersen, C.; Barrero, A. F. *J. Nat. Prod.* **2001**, *64*, 1590−1592.

(3) Takahashi, C.; Matsushita, T.; Doi, M.; Minoura, K.; Shingu, T.; Kumeda, Y.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2345−2353.

(4) (a) Barrow, C. J.; Sun, H. H. *J. Nat. Prod.* **1994**, *57*, 471−476. (b) Cascieri, M. A.; Macleod, A. M.; Underwood, D.; Shiao, L.-L.; Ber, E.; Sadowski, S.; Yu, H.; Merchant, K. J.; Swain, C. J.; Strader, C. D.; Fong, T. M. *J. Biol. Chem.* **1994**, *269*, 6587−6591.

(5) (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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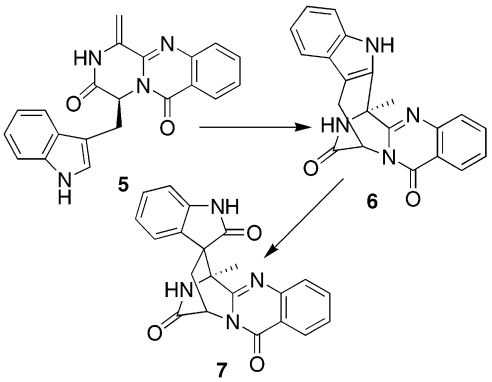
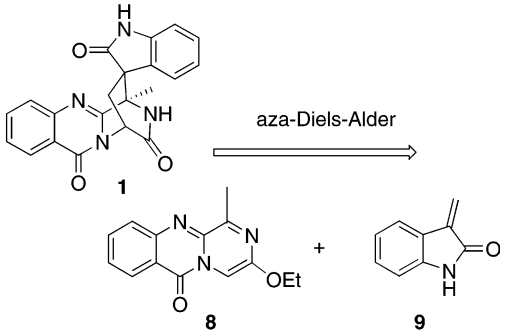
overall yield. Their elegant sequence is based on a biomimetic motif that employs as key steps the transannular iminium ion cyclization of indole **5** to **6** and subsequent NBS-mediated oxidative rearrangement[6] of the fused indole system in **6** to the spirocyclic structure of *ent*-alantrypinone (**7**).

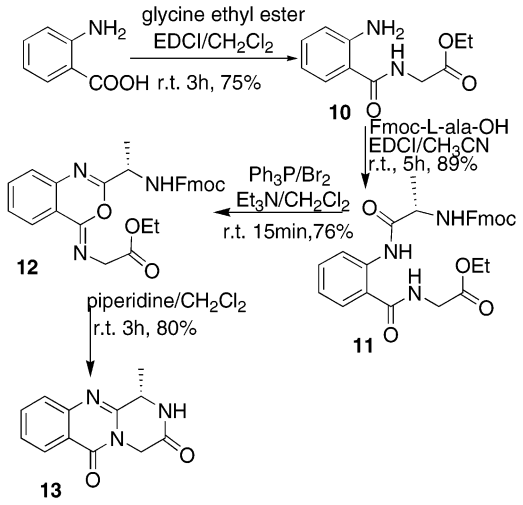


A fresh examination of the synthetic problem led us to explore whether alantrypinone (**1**) might be constructed by a hetero-Diels−Alder reaction of the hypothetical azadiene **8** with the known 3-methyleneoxindole **9**.[7]



To our knowledge, the fully conjugated 6*H*-pyrazino-[2,1-*b*]quinazoline-6-one system represented by structure **8** had not been reported in the literature. Its stability was unclear, and its propensity to serve as a diene in a Diels−Alder reaction was uncertain. To exploit this opportunity, we explored synthetic access to this interesting azadiene system. Our proposed key intermediate was the tricyclic dione **13**, previously described by Hernandez et al.[8] In a modification of their published route, anthranilic acid was condensed with ethyl glycinate, using EDCI to give the amide **10** (Scheme 1). A second coupling with Fmoc-L-ala-OH and EDCI in CH_3CN yielded the protected diamide **11**. Dehydrative cyclization of this diamide was achieved by using Ph_3P and Br_2 at room temperature to produce the imino benzoxazine **12**,[9] which on reaction with piperidine[10] resulted

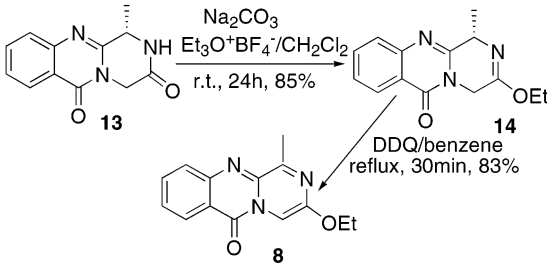
Scheme 1



in deprotection and cyclization to give the key intermediate **13** in 41% overall yield from anthranilic acid.

Dehydroaromatization of the dihydropyrazinone ring of dione **13** proved to be somewhat refractory. Treatment of **13** under diverse oxidative conditions (e.g. Br_2, NBS, SeO_2) led to mixtures or destruction of the molecule. An attempted oxidative chlorination with PCl_5 gave small amounts of a chloro derivative, which appeared to be the 3-chloro analogue of the desired **8**, but this substance was unstable and the process was not reproducible. Success in this transformation was finally achieved (Scheme 2) by reaction of dione **13**

Scheme 2



with triethyloxonium fluoborate in CH_2Cl_2 to give the imino ether **14**, which was gently oxidized by DDQ in benzene to produce the new azadiene **8** in 71% overall yield.[11] Diene **8** was purified by flash chromatography and obtained as a reasonably stable crystalline substance melting at 148−149 °C.

The dienophile 3-methyleneoxindole (**9**) was synthesized by the method of Rossiter.[12] To obtain pure **9** in high yield we found it essential to repeatedly wash a methylene chloride

(6) Pellegrini, C.; Strassler, C.; Weber, M.; Borschberg, H.-J. *Tetrahedron*: *Asymmetry* **1994**, *5*, 1979−1982.

(7) A possible Diels−Alder approach to the synthesis of **1** is alluded to in a footnote to the full paper by Hart and Magomedov cited as ref 5 above.

(8) Hernandez, F.; Buenadicha, F. L.; Avendano, C.; Sollhuber, M. *Tetrahedron*: *Asymmetry* **2001**, *12*, 3387−3398.

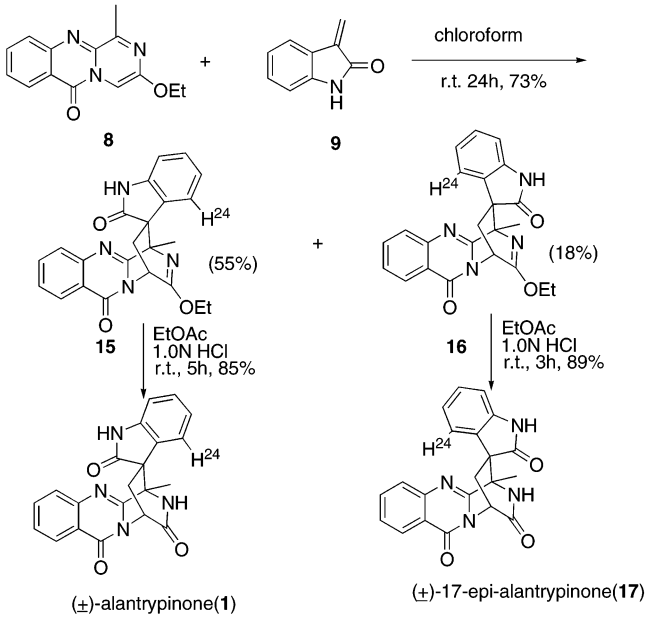
(9) Mazurkiewicz, R. *Monatsh. Chem.* **1989**, *120*, 973−980.

(10) (a) Snider, B. B.; Zeng, H. *Org Lett.* **2000**, *2*, 4103−4106. (b) He, H.; Snider, B. B. *J. Org Chem.* **1999**, *64*, 1397−1399.

(11) For a related aromatization see: Blake, K. W.; Porter, A. E. A.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2494−2497.

(12) Rossitter, S. *Tetrahedron Lett.* **2002**, *43*, 4671−4673.

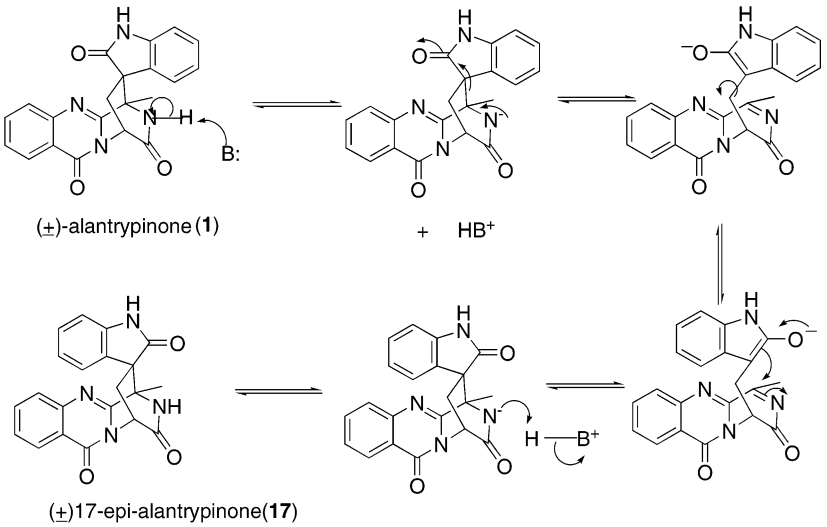
Scheme 3



extract of the final reaction mixture with saturated aqueous sodium bicarbonate to neutralize traces of acid. The aza-Diels−Alder reaction between diene **8** and dienophile **9** proceeded smoothly in chloroform at room temperature to produce a chromatographically separable mixture of adduct **15** in 55% yield and adduct **16** in 18% yield (Scheme 3). 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. The observed regiochemistry in adducts **15** and **16** paralleled that observed for some related cycloadditions,[13] and is consonant with the predominant direction of postulated dipolar contributors to the Diels−Alder transition state. It is of further interest that the major product **15** corresponds to an *exo* cycloaddition, a preference consistent with the observations of Langlois and Ghosez[14]and calculation by Sustmann and Sicking.[15] This *exo* stereochemistry of **15**, which corresponds to that of alantrypinone, is readily differentiated by ^{1}H NMR from that of its *endo* isomer **16** by the chemical shift of the C(24) aromatic proton ortho to the spirocyclic center. Whereas in **15** this signal comes at δ 6.81, in **16** that signal is at δ 5.87 because of the anisotropic shielding by the quinazoline π system. These structural assignments were confirmed by mild acid hydrolysis of adduct **15** and adduct **16** to yield respectively (±)-alantrypinone (**1**) and (±)-17-*epi*-alantrypinone (**17**). Our synthetic (±)-alantrypinone showed ^{1}H NMR and ^{13}C NMR spectra in agreement with the data reported in the literature.[1,5] The ^{1}H NMR of the 17-epimer again displayed the diagnostic upfield signal of H(24) at δ 5.95, in contrast to that of alantrypinone at δ 7.16.

Although the stereochemical ratio of **16** to **15** in our Diels−Alder sequence thus favored the natural series, we envisioned the possibility that this ratio could be enhanced by thermal equilibration of 17-*epi*-alantrypinone to the natural isomer. When a dioxane or d_6-DMSO solution of **17** was heated overnight to 100 °C, no conversion to **1** was observed. However, when **17** in d_6-DMSO was treated with 0.1 equiv of DBU and held at 100 °C for 45 min, approximately 60% of **17** was converted into **1**, and after 1.5 h some 75% of **1** was produced. Likewise, when (±)-alantrypinone was heated for 2.5 h under the same conditions, a 3:1 ratio of **1** to **17** was again generated. This DBU-catalyzed equilibration did not occur at 100 °C in dioxane, and the reaction in d_6-DMSO 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 4.[16]

Scheme 4



We have thus achieved a concise total synthesis of (±)-alantrypinone by a hetero-Diels−Alder strategy leading from anthranilic acid to racemic **1** in 8 steps and 13.5% overall yield. The regioselective and *exo*-selective cycloaddition of 3-methyleneoxindole and the novel azadiene **8** has been observed, and the facile anionic equilibration between **1** and **17** has been demonstrated. Further studies on the scope of Diels−Alder additions to **8** and extensions of the epimerization reaction at C(17) are under investigation.

Supporting Information Available: Data including ^{1}H NMR and ^{13}C NMR spectra for **1**, **8**, **13**, **15**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Pouilhes, A.; Langlois, Y.; Nshimyumukiza, P.; Mbiya, K.; Ghosez, L. *Bull. Soc. Chim. Fr*. **1993**, *130*, 304−309.

(15) Sustmann, R.; Sicking, W. *Tetrahedron* **1992**, *48*, 10293−10300.

(16) For a somewhat 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 calling this reference to our attention.