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Acid-Catalyzed Aza-Diels−Alder Reactions for the Total Synthesis of (±)-Lapatin B

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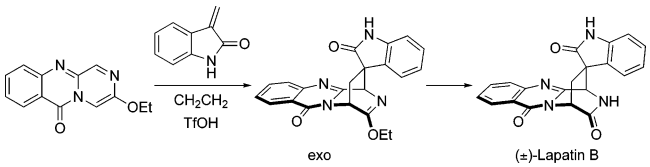
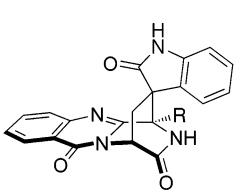
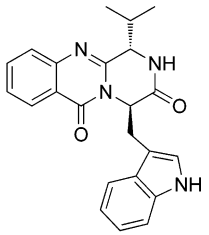


A 5-step total synthesis of microfungal alkaloid (±)-lapatin B has been accomplished via a key 2-aza-Diels−Alder reaction. Brønsted acids catalyze the cycloaddition step and provide improved exo selectivity. This synthetic route has been applied to the construction of related spiro-quinazoline structures.

(+)-Alantrypinone (**1**) and (−)-serantrypinone (**2**) are naturally occurring alkaloids that have been isolated from the microfungi of the genera *Aspergillus* and *Penicillium* by the groups of Larsen and Ozoe.[1] Both **1** and **2** have been reported to exhibit insecticidal acitivty against green peach aphids.[1c,d] These alkaloids belong to the larger class of quinazolinone based natural products[2,3] that are often bioactive, as is the case of substance P inhibitor fiscalin B (**4**).[4] The intricate spirocyclic structures of alantrypinone (**1**) and serantrypinone (**2**), containing two contiguous quaternary centers, represent attractive targets.




Fiscalin B (**4**)

Two total syntheses of alantrypinone have been reported thus far.[5] In particular, Kende et al. accomplished an efficient and convergent synthesis of (±)-alantrypinone using a hetero-Diels−Alder reaction between the 3-methyleneoxindole **6** and the azadiene **7** in the key step (Scheme 1).[5c,d]

We became interested in the study of this reaction to obtain easy access to various analogues of alantrypinone, including the recently isolated (−)-lapatin B (**3**).[6]

To have selective access to the desired cycloaddition diastereomer, various ways of improving the exo selectivity were investigated. We report here experimental studies that allowed us to achieve the first total synthesis of (±)-lapatin B.

Preparation of the Diels−Alder partners was straightforward. The methyleneoxindole **6** was obtained in two steps with good purity starting from isatine.[7] The synthesis of azadienes **7**−**9** required three steps (Scheme 2). The pyrazino[2,1-*b*]quinazoline-3,6-diones **10**−**12** were prepared following Liu's microwave mediated procedure.[8] Although moderate yields were obtained, this one-pot procedure represents a convenient alternative to the three-step preparation of quinazolines.[5c,d,9] Moreover, it appeared to be the only method allowing the preparation of **10**. Iminoether formation, followed by DDQ oxidation afforded the azadienes **7**−**9** in moderate to good yields.[10]

The stage was now set for the investigation of the hetero-Diels−Alder reaction. Azadiene **7** reacts with 1.2 equiv of methyleneoxindole **6** in chloroform at room temperature for 1 h to give the endo cycloadduct **17** as the major diastereomer with a 63:37 selectivity (Scheme 3). In agreement with Kende's work, thermal equilibration could not be established.[11]

In order to effect exo selectivity, we first turned our attention to the solvent.[12] The effects of solvent polarity on cycloaddition stereoselectivity were investigated both computationally and

(1) (a) Larsen, T. O.; Frydenvang, K.; Frisvad, J. C.; Christophersen, C. *J. Nat. Prod.* **1998**, *61*, 1154−1157. (b) Ariza, M. R.; Larsen, T. O.; Petersen, B. O.; Duus, J. O.; Christophersen, C.; Barrero, A. F. *J. Nat. Prod.* **2001**, *64*, 1590−1592. (c) Kuriyama, T.; Kakemoto, E.; Takahashi, N.; Imamura, K.; Oyama, K.; Suzuki, E.; Harimaya, K.; Yaguchi, T.; Ozoe, Y. *J. Agric. Food Chem.* **2004**, *52*, 3884−3887. (d) Ozoe, Y.; Takahashi, N.; Oyama, K.; Imamura, K.; Harimaya, T.; Yaguchi, T. J. Patent 2002142795.

(2) For a recent review, see: Mhaske, S. B.; Argade, N. O. *Tetrahedron* **2006**, *62*, 9787−9826.

(3) For total syntheses of this class of quinazolines, see: (a) He, F.; Snider, B. B. *Synlett* **1997**, 483−484. (b) Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432−2433. (c) Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 1022−1030. (d) Hernandez, F.; Lumetzberger, A.; Avendaño, C.; Söllhuber, M. *Synlett* **2001**, 1387−1390. (e) Snider, B. B.; Zeng, H. *J. Org. Chem.* **2003**, *68*, 545−563.

(4) Wong, S. M.; Musza, L. L.; Kydd, G. C.; Kullnig, R.; Gillum, A. M.; Cooper, R. *J. Antibiot.* **1993**, *46*, 545−553.

(5) (a) Hart, D. J.; Magomedov, N. A. *Tetrahedron Lett.* **1999**, *40*, 5429−5432. (b) Hart, D. J.; Magomedov, N. A. *J. Am. Chem. Soc.* **2001**, *123*, 5892−5899. (c) Kende, A. S.; Fan, J.; Chen, Z. *Org. Lett.* **2003**, *5*, 3205−3208. (d) Chen, Z.; Fan, J.; Kende, A. S. *J. Org. Chem.* **2004**, *69*, 79−85.

(6) (−)-Lapatin B was isolated from the microfungus *Penicillium lapataye:* Larsen, T. O.; Petersen, B. O.; Duus, J. O.; Sorensen, D.; Frisvad, J. C.; Hansen, M. E. *J. Nat. Prod.* **2005**, *68*, 871−874.

(7) Rossiter, S. *Tetrahedron Lett.* **2002**, *43*, 4671−4673.

(8) Liu, J.-F.; Ye, P.; Zhang, B.; Bi, G.; Sargent, K.; Yu, L.; Yohannes, D.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 6339−6345.

(9) Hernandez, F.; Buenadicha, F. L.; Avendaño, C.; Söllhuber, M. *Tetrahedron*: *Asymmetry* **2001**, *12*, 3387−3398.

(10) The modest yield obtained for the unsubstituted azadiene **8** may be due to its lower stability compared to **7** and **9**.

(11) When a sample of endo cycloadduct **17** was refluxed in dichlorobenzene for 2 days, no conversion to the exo product **16** was observed. The same result was obtained in chloroform in the presence of methyleneoxindole **6**.

(12) Sustmann, R.; Sicking, W.; Lamy-Schelkens, H.; Ghosez, L. *Tetrahedron Lett.* **1991**, *32*, 1401−1404.

10.1021/jo0705162 CCC: $37.00
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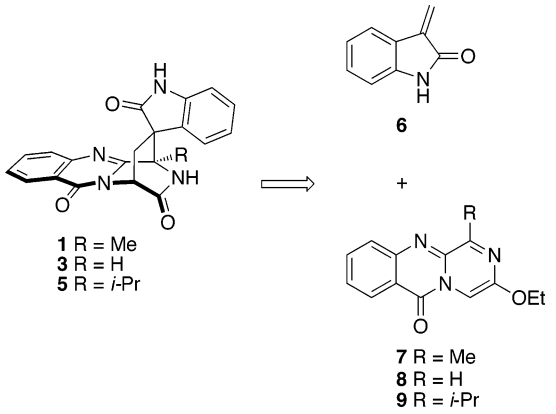
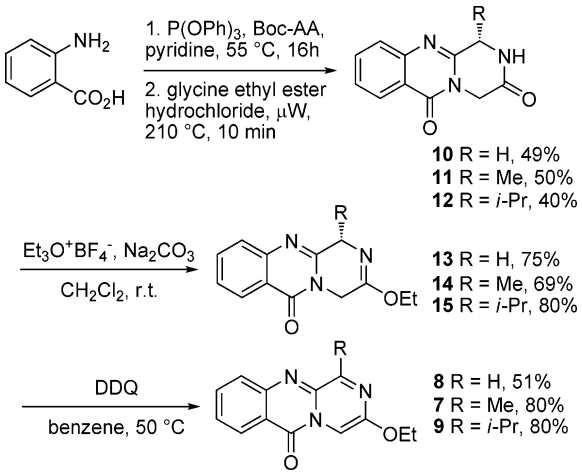
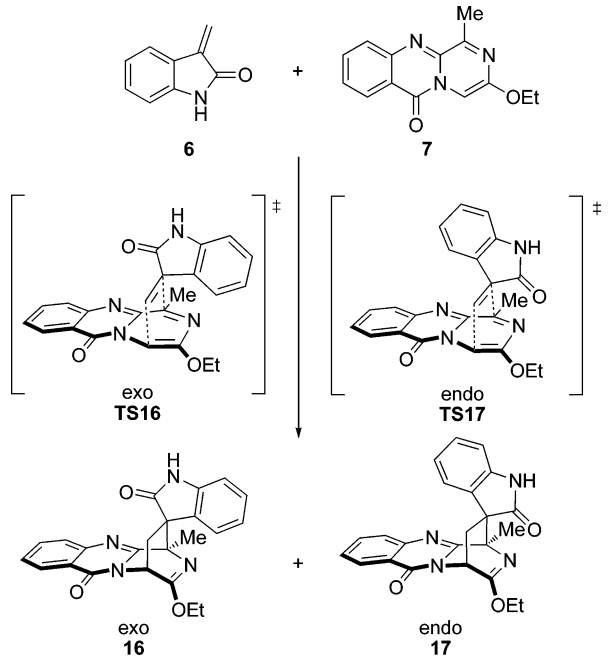
SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Preparation of Dienes 7, 8, and 9

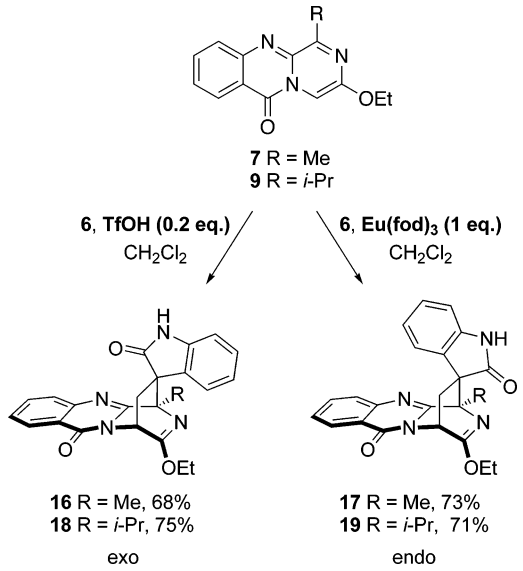


SCHEME 3. Diels−Alder Reaction between 6 and 7



experimentally. Free energies of solvation for transition states **TS16** and **TS17** (Scheme 3) were evaluated.[13] The preference for endo **TS17** is predicted to decrease significantly from 1.9 kcal/mol in the gas phase to 0.5 kcal/mol in chloroform. A change to the more polar solvent, acetonitrile, is predicted to enhance exo selectivity, with the activation enthalpy difference becoming 0.1 kcal/mol. As the polarity of the medium is increased, the exo structures are strongly stabilized with respect to the endo. In agreement, experimental exo:endo ratios of 37:63, 48:52, and 68:32 were found in chloroform, dichloromethane, and acetonitrile, respectively.

SCHEME 4. Tunable Stereoselectivity of the Diels−Alder Reaction



Lewis acid additives are known to have an influence on Diels−Alder stereoselectivity.[14] In our study, most of the Lewis acids gave a medium to good selectivity in favor of the exo diastereomer. In contrast, $Yb(OTf)_3$ induced a 72:28 endo:exo ratio, and more remarkably, $Eu(fod)_3$ led to a complete endo selectivity (Scheme 4). The strong exo selectivity observed with $La(OTf)_3$ was intriguing because it is opposite to that obtained with $Yb(OTf)_3$.[15] However, when varying the supplier of $La(OTf)_3$, an endo selectivity similar to the one obtained with $Yb(OTf)_3$ was observed. These results led us to believe that in some cases, contaminant triflic acid might have been be responsible for the observed exo selectivity. Accordingly, 0.2 equiv of triflic acid, at −20 °C, gave the exo iminoether **16** in high selectivity and with 68% yield. Lewis or Brønsted acids thus provide the endo or exo cycloadduct selectively.

With this improved Diels−Alder stereoselectivity in hand, we turned our attention to the two related azadienes **8** and **9**. The reaction of **9** in chloroform led to a 2:1 endo:exo selectivity.[16] With triflic acid catalysis, we were pleased to observe a complete selectivity toward **18**, which was isolated in 75% yield. As in the case of the diene **7**, the use of $Eu(fod)_3$ allowed the inversion of selectivity in favor of the endo adduct **19** obtained in 71% yield (Scheme 4).[17]

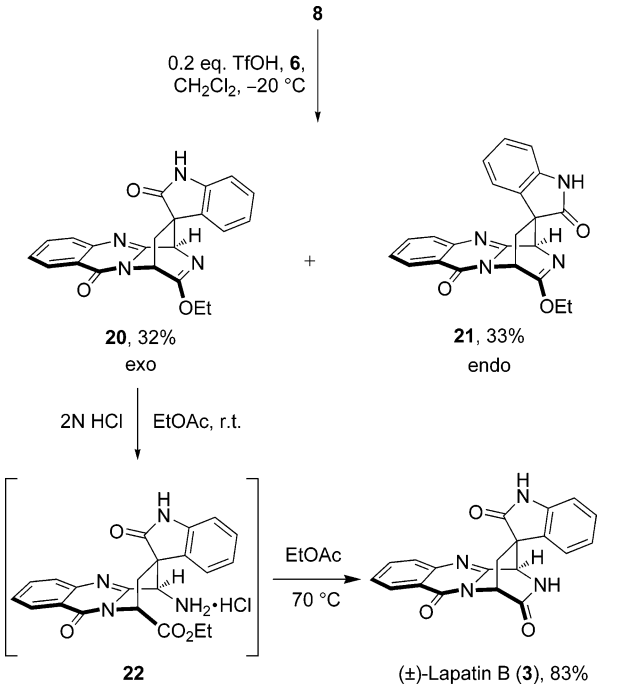
(13) B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) energies with PCM solvent corrections. See the Supporting Information.

(14) (a) Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617−2618 and references cited therein. (b) Lamy-Schelkens, H.; Giomi, D.; Ghosez, L. *Tetrahedron Lett.* **1989**, *30*, 5887−5890.

(15) Both lanthanide triflates are known to induce similar selectivities in Diels−Alder reactions: Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227−2302.

(16) One equivalent of diene **9** was reacted with 1.2 equiv of **6** in chloroform overnight at room temperature.

SCHEME 5. (±)-Lapatin B: Improved Selectivity and End-Game



In contrast to **7** and **9**, the unsubstituted diene **8** proved to be more challenging. When azadiene **8** was submitted to 1.2 equiv of methyleneoxindole **6**, a strong endo selectivity (7:1) was observed. However, in the presence of triflic acid, a 1:1 endo:exo ratio could be restored. This improved exo selectivity was consistent with the results obtained for **7** and **9**, allowing for the isolation of exo adduct **20** for the synthesis of (±)-lapatin B (**3**) (Scheme 5).

Hydrolysis of **20** in the presence of 1 equiv of 2 N HCl in ethyl acetate led to the precipitation of water-soluble salt **22** instead of lapatin **3**, a result of the opening of the lactam.[18] However, when the reaction mixture was further heated for 1.5 h, **22** cyclized affording (±)-lapatin B in 83% yield.

In conclusion, we have shown that the improvement in the key Diels−Alder step, combined with a concise synthesis of the 2-azadiene precursor, provides an elegant access to both diastereomers of (±)-alantrypinone and analogues. This methodology allowed us to report the first total synthesis of (±)-lapatin B in only 5 steps in 8% overall yield.

Experimental Section

General Procedure for the Synthesis of 2,4-Dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones (10−12). A mixture of anthranilic acid (2.74 g, 20 mmol), *N*-Boc-amino acid (20 mmol, 1 equiv), and triphenyl phosphite (5.77 mL, 22 mmol, 1.1 equiv) in pyridine (30 mL) was heated for 16 h at 55 °C. The reaction mixture was cooled and glycine methyl ester hydrochloride (2.51 g, 20 mmol, 1 equiv) was added. The resulting mixture was dispatched into microwave adapted vials and each one of them was irradiated for 10 min, at a temperature of ∼210 °C. The reaction mixtures were then combined and concentrated in vacuo, and the residue was purified by silica gel flash chromatography (using a gradient from a 1:1 mixture of CH_2Cl_2:EtOAc to a 50:50:5 CH_2Cl_2:EtOAc:MeOH mixture as eluent).

2,4-Dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (10): white solid (2.11 g, 49%); mp 278−280 °C. MS (API-ES, positive), 216 (M + 1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (br s, 1H), 8.11 (dd, 1H, J = 1.1, 7.7 Hz), 7.82 (ddd, 1H, J = 1.4, 7.3, 8.4 Hz), 7.63 (d, 1H, J = 7.7 Hz), 7.52 (dd, 1H J = 7.0, 8.1 Hz), 4.52 (s, 2H), 4.42 (d, 2H, J = 2.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.1, 159.8, 150.1, 147.1, 134.7, 126.8, 126.7, 126.2, 119.7, 44.8, 44.7; HRMS (DCI/NH_3) calcd for $C_{11}H_{10}N_3O_2$ *m*/*z* 216.0768, found 216.0763.

General Procedure for the Synthesis of Iminoethers 13−15. To a solution of the quinazoline (**10−12**) (3 mmol) in anhydrous CH_2Cl_2 (200 mL), under argon, were added anhydrous sodium carbonate (1.95 g, 18.0 mmol) and triethyloxonium tetrafluoroborate (870 mg, 4.5 mmol). The mixture was stirred at room temperature for 24 h. The solid was filtered and the resulting filtrate was washed with saturated aqueous sodium carbonate solution and brine and dried over $MgSO_4$. After evaporation of the solvent the crude material was purified by flash chromatography (SiO_2, hexane:EtOAc 1:1).

Iminoether 13: white solid (546 mg, 75%); mp 152−155 °C. MS (API-ES, positive), 244 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, 1H, J = 1.2, 8.0 Hz), 7.77 (ddd, 1H, J = 1.4, 7.0, 8.4 Hz), 7.67 (dd, 1H, J = 1.2, 8.1 Hz), 4.76 (AB, 2H, J_{AB} = 1.4, 2.0 Hz), 4.58 (AB, 2H, J_{AB} = 1.8, 1.9 Hz), 4.70 (q, 2H, J = 7.4 Hz), 1.35 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 160.0, 150.3, 147.5, 134.7, 126.9, 126.7, 120.0, 62.1, 40.7, 51.5, 14.5; HRMS (DCI/NH_3) calcd for $C_{13}H_{14}N_3O_2$ *m*/*z* 244.1081, found 244.1078.

General Procedure for the Synthesis of 2-Aza-Dienes 7−9. To a solution of the iminoether (**13−15**) (3 mmol, 1 equiv) in benzene (55 mL), at 50 °C, was added slowly a solution of DDQ (750 mg, 3.3 mmol, 1.1 equiv) in benzene (22 mL). After the reaction was complete, the reaction mixture was cooled and filtered through neutral alumina (the alumina was rinsed several times with CH_2Cl_2). When necessary, a further purification by flash chromatography was performed (SiO_2, CH_2Cl_2:EtOAc 90:10).

2-Aza-diene 8: yellow solid (369 mg, 51%); mp 129−130 °C. MS (API-ES, positive), 242 (M + 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.49 (d, 1H, J = 7.8 Hz), 8.07 (s, 1H), 7.92 (d, 1H, J = 4.2 Hz), 7.61 (m, 2H), 4.29 (q, 2H, J = 7.3 Hz), 1.52 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 153.1, 152.4, 147.7, 139.5, 127.9, 127.1, 127.0, 134.9, 117.0, 97.3, 64.4, 14.6; HRMS (DCI/NH_3) calcd for $C_{13}H_{12}N_3O_2$ *m*/*z* 242.0924, found 242.0925.

General Procedure for the Lewis Acid-Catalyzed Aza-Diels−Alder Reactions. Eu(fod)$_3$ (143 mg, 0.14 mmol, 1 equiv) was added to a solution of the aza-dienes (**7−9**) (0.14 mmol) in CH_2Cl_2 (4 mL) at room temperature. After 1 min, methyleneoxindole (24 mg, 0.17 mmol, 1.2 equiv) was added. The reaction was complete after 16 h. The reaction was then quenched with an aqueous saturated solution of sodium bicarbonate. The aqueous phase was extracted three times with EtOAc. The organic layers were combined, washed with brine, and dried over sodium sulfate. After evaporation, the crude was purified by flash chromatography (SiO_2, 9:1 to 8:2 hexane:EtOAc gradient).

General Procedure for Brønsted Acid-Catalyzed Aza-Diels−Alder Reactions. TfOH (4 μL, 0.2 equiv) was added to a solution of the aza-dienes (**7−9**) (0.17 mmol) in CH_2Cl_2 (2.5 mL) at −20 °C. After 1 min, methyleneoxindole (29 mg, 0.2 mmol, 1.2 equiv) was added. The reaction was complete after 1 h. The reaction was then quenched with an aqueous saturated solution of sodium bicarbonate. The aqueous phase was extracted three times with EtOAc. The organic layers were combined, washed with brine, and dried over sodium sulfate. After evaporation, the crude was purified by flash chromatography (SiO_2, 8:2 to 7:3 hexane:EtOAc gradient).

(17) In both cases, the selectivity was superior to 98:2. Hydrolysis of **16−19** in the presence of 1 equiv of aqueous 2 N HCl in ethyl acetate afforded the corresponding amides, see the Supporting Information.

(18) This phenomenon was not observed in the hydrolyses of **16** and **18**.

Exo Iminoether 20. Following the Brønsted acid-catalyzed aza-Diels−Alder general procedure, **20** was isolated as the minor product of the reaction between diene **8** and methyleneoxindole **6**. White solid (37 mg, 32%); mp 277−278 °C. MS (API-ES, positive), 387 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, 1H, J = 1.0, 7.1 Hz), 8.27 (s, 1H), 7.74 (m, 1H), 7.68 (d, 1H, J = 7.3 Hz), 7.48 (m, 1H), 7.22 (td, 1H, J = 1.5 and 7.7 Hz), 7.05 (dd, 1H, J = 1.5, 7.7 Hz), 7.02 (ddd, 1H, J = 1.1, 7.3, 7.7 Hz), 6.76 (d, 1H J = 7.7 Hz), 6.06 (dd, 1H, J = 2.4, 3.1 Hz), 4.85 (s, 1H), 4.38 (m, 2H), 2.57 (B of ABX, 1H, J_{AB} = 13.8 Hz, J_{BX} = 3.1 Hz), 2.20 (A of ABX, 1H, J_{AB} = 13.6 Hz, J_{AX} = 2.4 Hz), 1.44 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 172.7, 159.4, 154.2, 147.6, 141.3, 134.2, 130.8, 128.9, 127.6, 127.0, 126.9, 124.4, 122.8, 120.7, 110.2, 65.9, 64.0, 51.1, 48.3, 36.0, 14.2; HRMS (DCI/NH_3) calcd for $C_{22}H_{19}N_4O_3$ *m*/*z* 387.1452, found 387.1449.

Endo Iminoether 21. Following the Brønsted acid-catalyzed aza-Diels−Alder general procedure, **21** was isolated as the major product of the reaction between diene **8** and methyleneoxindole **6**. White solid (38 mg, 33%); mp 165−170 °C. MS (API-ES, positive), 387 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, 1H, J = 1.1, 8.1 Hz), 8.13 (s, 1H), 7.79 (ddd, 1H, J = 1.5, 7.3, 8.1 Hz), 7.66 (dd, 1H, J = 7.7 Hz), 7.48 (ddd, 1H, J = 1.1, 7.0, 8.5 Hz), 7.17 (ddd, 1H, J = 1.1, 7.7, 8.1 Hz), 6.87 (d, 1H, J = 7.7 Hz), 6.75 (ddd, 1H, J = 1.1, 6.7, 7.7 Hz), 6.07 (m, 1H), 5.98 (d, 1H, J = 7.3 Hz), 4.86 (s, 1H), 4.39−4.47 (m, 1H), 4.25−4.33 (m, 1H), 2.54 (B of ABX, 1H, J_{AB} = 13.9 Hz, J_{BX} = 2.2 Hz), 2.26 (A of ABX, 1H, J_{AB} = 13.9 Hz, J_{AX} = 3.3 Hz), 1.42 (dd, 3H, J = 7.0, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 172.3, 158.9, 151.9, 147.2, 140.6, 134.8, 129.3, 129.2, 127.8, 127.3, 127.0, 123.6, 122.6, 120.5, 110.0, 66.0, 64.1, 49.7, 48.5, 35.0, 14.0; HRMS (DCI/NH_3) calcd for $C_{22}H_{19}N_4O_3$ *m*/*z* 387.1452, found 387.1449.

Exo Ammonium Chloride 22. Exo Iminoether **20** (22.3 mg, 0.058 mmol) was dissolved in 1.0 mL of EtOAc, and 1.05 equiv of 2 N HCl (30 μL) was added at room temperature. A precipitate was observed and filtered to give salt **22** in 60% yield (15.2 mg) as a white solid: decomposition at 235 °C. MS (API-ES, positive), 405 (M + 1). ^{1}H NMR (500 MHz, MeOD) δ 8.28 (dd, 1H, J = 1.0, 8.1 Hz), 7.93 (ddd, 1H, J = 1.5, 7.4, 8.4 Hz), 7.85 (d, 1H, J = 7.9 Hz), 7.66 (m, 1H), 7.34 (ddd, 1H, J = 1.0, 7.7, 8.0 Hz), 7.07 (d, 1H, J = 7.7 Hz), 7.01 (d, 1H, J = 7.0 Hz), 5.58 (m, 1H), 6.93 (m, 1H), 3.96 (m, 2H), 3.04 (B of ABX, 1H, J_{AB} = 15.0 Hz, J_{BX} = 8.8 Hz), 2.65 (A of ABX, 1H, J_{AB} = 15.0 Hz, J_{AX} = 1.4 Hz), 0.95 (t, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, MeOD) δ 178.2, 14.0, 169.7, 163.1, 149.0, 147.0, 143.6, 136.6, 131.7, 129.5, 128.6, 127.8, 127.8, 123.9, 123.2, 121.7, 112.2, 63.4, 54.0, 53.2, 50.3, 33.5.

(±)-Lapatin B (3). Iminoether **20** (20 mg, 0.052 mmol) was dissolved in 2.0 mL of EtOAc, and 1 equiv of 2 N HCl (25 μL) was added at room temperature. After 30 min at room temperature, the reaction mixture was refluxed for 90 min (LCMS analysis showed completion of the reaction). Nine milligrams of lapatin B (**3**) were isolated by filtration. The filtrate was quenched with a saturated solution of sodium carbonate, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with water and dried over sodium sulfate. After concentration, an additional 6.4 mg of **3** were isolated and the global yield was 83% as a white solid: mp 285 °C. MS (API-ES, positive), 387 (M + 1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.69 (s, 1H), 9.64 (m, 1H), 8.21 (dd, 1H, J = 1.0, 8 Hz), 7.86 (m, 1H), 7.66 (d, 1H, J = 7.8 Hz), 7.59 (m, 1H), 7.30 (ddd, 1H, J = 1.5, 7.6, 8.1 Hz), 7.19 (d, 1H, J = 7.2 Hz), 7.08 (m, 1H), 6.93 (d, 1H, J = 7.6 Hz), 5.55 (m, 1H), 4.32 (d, 1H, J = 5.4 Hz), 2.39 (d, 2H, J = 2.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 176.6, 169.5, 158.3, 151.2, 147.1, 134.8, 141.9, 130.7, 129.1, 127.4, 127.2, 126.4, 124.1, 122.1, 120.4, 110.1, 52.7, 59.0, 51.2, 34.8; HRMS (DCI/NH_3) calcd for $C_{20}H_{15}N_4O_3$ *m*/*z* 359.1139, found 359.1139.

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Supporting Information Available: Results from the computational study on the cycloaddition transition states **TS16** and **TS17**, including energies and Cartesian coordinates of the optimized structures, experimental synthetic procedures, and solvent effect experiments, as well as characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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