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Thermal 1,3-Trityl Migrations in Diels−Alder Domino Reactions of 1-Trityl-4-vinyl-1*H*-imidazoles

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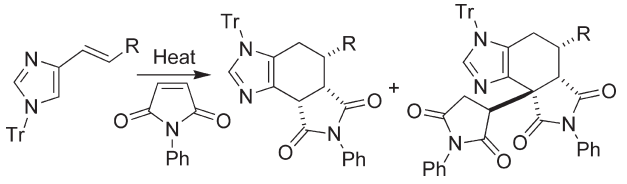

Under thermal conditions, tritylimidazoles have been shown to undergo sterically driven N→N trityl migrations, in disagreement with previously published reports. These migrations are a key step in several highly diastereoselective domino reaction sequences (Diels−Alder, [1,3]-H shift, [1,3]-trityl migration and Diels−Alder, [1,3]-H shift, [1,3]-trityl migration, Michael reaction) leading to architecturally complex molecules.

Diels−Alder (D−A) and hetero-Diels−Alder (h-D−A) reactions have long been used in both synthetic[1] and biosynthetic[2] approaches for the construction of complex natural product architectures. Within this field, vinyl-substituted heteroaromatics have been utilized extensively as dienes in inter- and intramolecular D−A and h-D−A reactions.[3−7]

D−A dimerization reactions of both vinylimidazoles and vinylindoles have been implicated in the biosynthesis of a number of marine alkaloids such as ageliferin (isolated from the sponge *Agelas coniferin*)[8] and cyclo-aplysinopsin A (isolated from an unidentified dendrophylliid coral from the Comoros islands).[9] These compounds may arise via head-to-head (ageliferin) or head-to-tail (cyclo-aplysinopsin A) D−A reactions followed by rearomatization of the heteroaromatic component (Figure 1).[10]

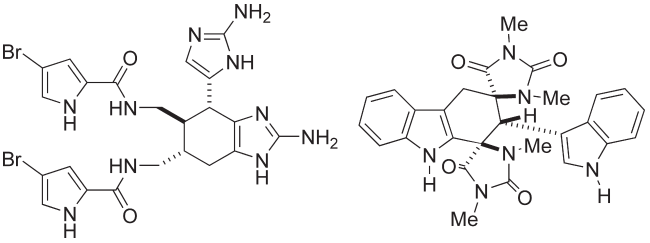

FIGURE 1. Ageliferin and cyclo-aplysinopsin A.

As part of an extensive investigation into the synthesis and biosynthesis of ageliferin (and related oroidin alkaloids), several research groups have examined the D−A reactions of a range of 3- and 4-vinyl-substituted imidazoles,[5] as well as the D−A reactions of imidazolones.[6]

These reports not only provided a valuable insight into alkaloid synthesis and biosynthesis but also contained discussion of a number of intriguing and unexpected byproducts arising from D−A initiated domino reactions.

Domino reactions are of increasing value in synthetic chemistry as they can allow the regio- and stereoselective construction of multiple C−C and C−X bonds in one reaction vessel. This leads to both highly efficient synthesis (through the minimization of isolation steps) and application through rapid library generation for use in medicinal chemistry and chemical biology.[11]

(1) Recent reviews: (a) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779–4807. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698. (c) Brocksom, T. J.; Nakamura, J.; Ferreira, M. L.; Brocksom, U. *J. Braz. Chem. Soc.* **2001**, *12*, 597–622.

(2) Oikawa, H.; Tokiwano, T. *Nat. Prod. Rep.* **2004**, *21*, 321–352.

(3) Selected vinylindole examples: (a) Bleile, M.; Otto, H.-H. *Monatsh. Chem.* **2005**, *136*, 1799–1809. (b) Le Strat, F.; Maddaluno, J. *Org. Lett.* **2002**, *4*, 2791–2793. (c) Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3189–3191. (d) Eitel, M.; Pindur, U. *J. Org. Chem.* **1990**, *55*, 5368–5374. (e) Eitel, M.; Pindur, U. *Heterocycles* **1988**, *27*, 2353–2362. (f) Gonzalez, E.; Pindur, U.; Schollmeyer, D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1767–1771. (g) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 7586–7593. (h) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1994**, *59*, 7197–7198. (i) Ohno, M.; Shimizu, S.; Eguchi, S. *Tetrahedron Lett.* **1990**, *31*, 4613–4616. (j) Joseph, B.; Da Costa, H.; Mérour, J.-Y.; Léonce, S. *Tetrahedron* **2000**, *56*, 3189–3196.

(4) Selected vinylpyrazole examples: (a) Sepúlveda-Arques, J.; Medio-Simón, M.; Piqueres-Vidal, L. *Monatsh. Chem.* **1989**, *120*, 1113–1118. (b) Medio-Simón, M.; Sepúlveda-Arques, J. S. *Tetrahedron* **1986**, *42*, 6683–6686.

(5) Selected vinylimidazole examples: (a) Lovely, C. J.; Du, H.; Rasika Dias, H. V. *Org. Lett.* **2001**, *3*, 1319–1322. (b) Lovely, C. J.; Du, H.; Rasika Dias, H. V. *Heterocycles* **2003**, *60*, 1–7. (c) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. *Org. Lett.* **2003**, *5*, 3623–3626. (d) Lovely, C. J.; Du, H.; He, Y.; Rasika Dias, H. V. *Org. Lett.* **2004**, *6*, 735–738. (e) Du, H.; He, Y.; Sivappa, R.; Lovely, C. J. *Synlett* **2006**, 965–992. (f) Lovely, C. J.; Du, H.; Sivappa, R.; Bhandari, M. R.; He, Y.; Rasika Dias, H. V. *J. Org. Chem.* **2007**, *72*, 3741–3749. (g) Sivappa, R.; Mukherjee, S.; Rasika Dias, H. V.; Lovely, C. J. *Org. Biomol. Chem.* **2009**, *7*, 3215–3218. (h) Pöverlein, C.; Breckle, G.; Lindel, T. *Org. Lett.* **2006**, *8*, 819–821. (i) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, *12*, 1753–1783.

(6) Selected vinylimidazolone examples: (a) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535–1538. (b) Poullennec, K.; Kelly, A. T.; Romo, D. *Org. Lett.* **2002**, *4*, 2645–2648. (c) Poullennec, K.; Romo, D. *J. Am. Chem. Soc.* **2003**, *125*, 6344–6345. (d) Dransfield, P. J.; Wang, S.; Dilley, A.; Romo, D. *Org. Lett.* **2005**, *7*, 1679–1682.

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(8) Rinehart, K. L. *Pure Appl. Chem.* **1989**, *61*, 525–528. Kobayashi, J.; Tsuda, M.; Murayama, T.; Nakamura, H.; Ohizuma, Y.; Ishibashi, M.; Iwamura, M.; Ohta, T.; Nozoe, S. *Tetrahedron* **1990**, *46*, 5579–5586. Williams, D. H.; Faulkner, D. J. *Tetrahedron* **1996**, *52*, 5381–5390.

(9) Mancini, I.; Guella, G.; Zibrowius, H.; Pietra, F. *Tetrahedron* **2003**, *59*, 8757–8762.

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(11) Domino reactions: Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. Domino reactions for natural products and medicinal chemistry: Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304–322. Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967–1983.

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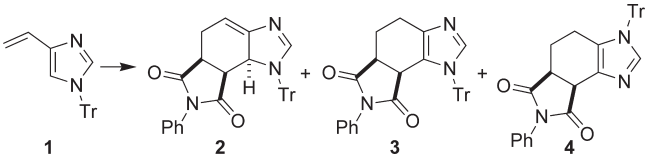
Thus inspired, we embarked upon an investigation of the D−A reactions of 4-vinyl-1*H*-imidazoles with a view to optimizing these reactions to selectively generate unusual domino reaction products in high yields.

Rapid routes to 4-vinylimidazoles from urocanic acid were based on the sterically controlled, selective trityl protection of 3-/4-substituted imidazoles. 1-Trityl-4-vinyl-1*H*-imidazole (**1**) was accessed via a literature approach involving thermal decarboxylation of urocanic acid and subsequent trityl protection of the 1 position (confirmation of the regiochemistry of **1** was achieved by single-crystal X-ray analysis, see the Supporting Information).[12,13]

Lovely et al. have previously reported the thermal D−A reaction of 1-trityl-4-vinyl-1*H*-imidazole (**1**) with *N*-phenylmaleimide (NPM).[5a,e,f] However, when we re-examined this reaction, under reaction conditions similar to those reported (heating in toluene or $CHCl_3$), we discovered that the reaction resulted in the formation of the expected D−A product **2** but only trace quantities of the rearomatized compound **3**. In addition, after prolonged reaction times we observed an unexpected N→N trityl migrated product **4** in moderate yield (Table 1).

TABLE 1. Reaction of 1 with NPM[a]



solvent	temp/°C	time/h	yield of **2**[b]/%	yield of **4**[b]/%
toluene	110	1	35	
toluene	110	3	78	
toluene	110	5		32
$CHCl_3$	61	16	28	6
$CHCl_3$	61	24	25	51

[a]Reaction conditions: 2.5 equiv of *N*-phenylmaleimide. [b]Isolated yields.

Confirmation of the structures of **3** and **4** was obtained through single-crystal X-ray analysis of the isolated compounds (see the Supporting Information). Unfortunately, all attempts to grow X-ray quality crystals of **2** only resulted in isolation of the rearomatized material **3**.[13]

On comparison with reported spectral data, we believe that the major compound **4** has been previously misassigned, due to the N→N trityl migration which has occurred. Thus, our spectral data for **4** matches data that have been erroneously attributed to a compound with structure **3**.[5a,e,f]

We submit that compound **1** undergoes a D−A reaction to give **2**, followed by a [1,3]-H migration to give **3**. Examination of the X-ray structure of **3** shows significant steric crowding of the newly formed 1-phenylpyrrolidine-2,5-dione ring by the trityl group, whereas in **4** the trityl group has migrated to give what appears to be a much less crowded molecule.

In an attempt to rationalize this migration event, structures **3** and **4** were modeled using a HF/3-21G* level of theory calculation, performed with Spartan.[14] The calculation showed that **4** is the thermodynamic product, being approximately 19 kJ mol^{-1} more stable than **3** (Figure 2).

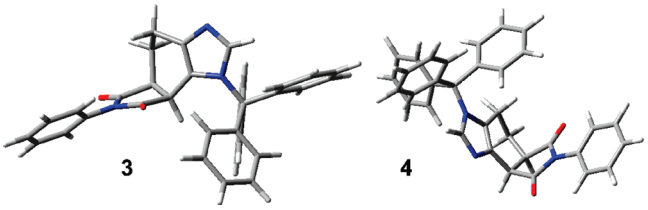


FIGURE 2. Hartree−Fock optimized structures for regioisomers **3** and **4**.

We hypothesized that the observed trityl migration might arise through addition of an electrophile/proton to the imidazole N lone pair of **3**, generating an imidazolium cation. Loss of a trityl cation followed by trapping by another molecule of **3** would result in a ditritylated imidazolium cation of **3**, which can in turn lose the most sterically hindered trityl to give **4** and propagate the reaction.

To explore this proposal, isolated **3** was heated to 45 °C in $CDCl_3$ and the reaction monitored by ^1H NMR. Clean conversion to **4** was observed after 14 h, along with the formation of protonated **4** arising from adventitious HCl. However, removal of HCl, via a $K_2CO_{3(aq)}$ wash of the reaction solvent, resulted in a considerable reduction in reaction rate.

N→C migrations in imidazole systems have previously been reported under flash vacuum pyrolysis conditions through concerted [1,5]-sigmatropic rearrangements of alkyl groups, from the N-1 to the C-5 position.[15] Under more standard reaction conditions, the N→N migrations of Bn, SEM, and MOM groups have recently been reported to occur with the addition of catalytic BnCl, SEMCl, or MOMCl, respectively, to give the least sterically hindered thermodynamic products.[16] However, this manuscript is, to our knowledge, the first report of trityl N→N migration under mild thermal conditions.

A common motif in the D−A chemistry of vinyl imidazoles involves the inclusion of a heteroatom-(N- or O-)-substituted methylene group at the vinyl terminus. These substrates have been examined in synthetic approaches to both ageliferin and several other related oroidin alkaloids.[5i] Thus, we decided to synthesize 4-((*E*)-3-((*tert*-butyl)dimethylsilyl)oxyprop-1-enyl)-1-trityl-1*H*-imidazole (**6**) to examine its potential for domino reactions under our conditions. Compound

(12) Synthesis of 4-vinyltritylimidazole: Faler, C. A.; Joullié, M. M. *Org. Lett.* **2007**, *9*, 1987–1990. Based on the original procedures: Overberger, C. G.; Glowaky, R. C.; Pacansky, T. J.; Sannes, K. N. *Macromol. Synth.* **1974**, *5*, 43–49. Burger, A.; Yost, W. L. *J. Am. Chem. Soc.* **1948**, *70*, 2198–2201. Data in agreement with: Kokosa, J. M.; Szafasz, R. A.; Tagupa, E. *J. Org. Chem.* **1983**, *48*, 3605–3607.

(13) The crystallographic coordinates of **1**, **3**, **4**, **7**, and **8** have been deposited with the Cambridge Crystallographic Data Centre, deposition nos. CCDC 768425, 768426, 768427, 768428, and 768429, respectively. These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223−336−033; or deposit@ccdc.cam.ac.uk).

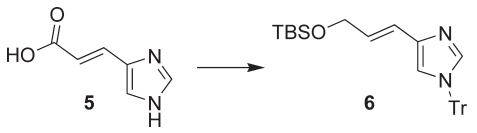
(14) Spartan '06 for Windows. Wavefunction, Inc.: Irvine, CA, 2006.

(15) N→C migrations: Begg, C. G.; Grimmett, M. R.; Wethey, P. D. *Aust. J. Chem.* **1973**, *26*, 2435–2446. Maquestiau, A.; Tommasetti, A.; Pedregal-Freire, C.; Elguero, J.; Flammang, R.; Wiersum, U. E.; Bender, H.; Wentrup, C. *J. Org. Chem.* **1986**, *51*, 306–309. Mitsuhashi, K.; Itho, E.-I.; Kawahara, T.; Tanaka, K. *J. Heterocycl. Chem.* **1983**, *20*, 1103–1105. N→C migrations of trityl: Giesemann, H.; Lettau, H.; Mannsfeldt, H.-G. *Chem. Ber.* **1960**, *93*, 570–576.

(16) N→N migrations: Kuroda, T.; Suzuki, F. *Tetrahedron Lett.* **1992**, *33*, 2027–2028. Moores, I. G.; Scriven, E. F. V.; Smalley, R. K.; Suschitzky, H. *J. Fluorine Chem.* **1988**, *41*, 277–288. He, Y.; Chen, Y.; Du, H.; Schmid, L. A.; Lovely, C. J. *Tetrahedron Lett.* **2004**, *45*, 5529–5532. Lovely, C. J.; Sivappa, R.; Mukherjee, S.; Doundoulakis, T.; Lima, H. M.; Yousufuddin, M. *Heterocycles* **2010**, *80*, 1353–1358.

6 was synthesized via methylation of urocanic acid (**5**), selective tritylation of the 1 position, DIBAL-H reduction to the primary alcohol, and TBS protection (Scheme 1).[17]

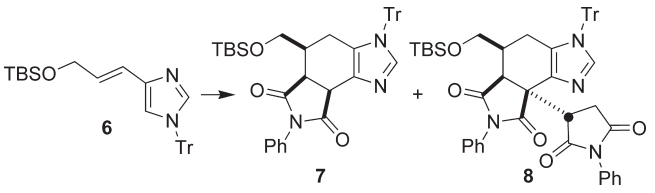
SCHEME 1. Synthesis of 6[a]



[a]Reaction conditions: (i) MeOH, $SOCl_2$, reflux, 16 h (81%); (ii) TrCl, Et_3N, THF, rt, 16 h (97%); (iii) 3 equiv of DIBAL-H, DCM, −78 °C, 1 h (67%); (iv) TBSCl, imidazole, DCM, 16 h (68%).

Under standard conditions, **6** reacts with NPM to give **7**, arising from an *endo*-D−A, [1,3]-H migration, [1,3]-Tr migration domino reaction sequence. However, with extended reaction times an additional compound **8** was also observed (Table 2). Again, confirmation of the structures of **7** and **8** was obtained through single-crystal X-ray analysis of the isolated compounds (see the Supporting Information).[13]

TABLE 2. Reaction of 6 with *N*-Phenylmaleimide[a]

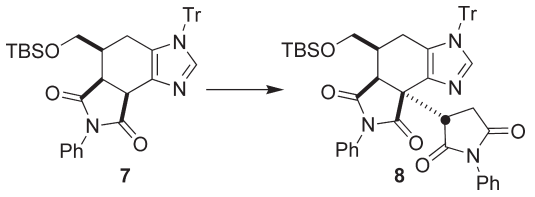


solvent	temp/°C	time/h	yield of **7**[b]/%	yield of **8**[b]/%
toluene	110	16	63	9
toluene	110	72	10	57

[a]Reaction conditions: 2.5 equiv of *N*-phenylmaleimide. [b]Isolated yields.

Unlike other reported 2:1 adducts, compound **8** did not arise through intermolecular ene reactions with additional NPM but instead through a previously unobserved Michael addition of the enol form of **7** to an NPM unit. We have demonstrated that compound **8** may be formed through such a Michael addition. Purified **7** was dissolved in $CDCl_3$, treated with 1 equiv of NaH, and quenched with D_2O. This led to selective deuteration of the tertiary carbon α to the imidazole ring. Thus, deprotonation of **7**, with NaH followed by addition of NPM, gave compound **8** in 61% isolated yield (Scheme 2).

SCHEME 2. Formation of 8 from 7 via Michael Addition[a]



[a]Reaction conditions: NaH, toluene, rt, 1 h, then NPM, reflux 6 h (61%).

(17) Dolensky, B.; Kirk, K. L. *J. Org. Chem.* **2002**, *67*, 3468–3473. Pirrung, M. C.; Pei, T. *J. Org. Chem.* **2000**, *65*, 2229–2230. Kosaka, K.; Maruyama, K.; Nakamura, H.; Ikeda, M. *J. Heterocycl. Chem.* **1991**, *28*, 1941–1944. Uenishi, J.; Motoyama, M.; Takahashi, K. *Tetrahedron: Asymmetry* **1994**, *5*, 101–110.

We have demonstrated a number of novel domino reaction routes for the rapid formation of complex molecules. For example, the formation of **8** generates four contiguous stereocenters, including a quaternary center, three new C−C bonds, and one C−N bond. Thus, this sets the scene for the construction of natural product scaffold libraries with potential medicinal chemistry application. We have also shown a facile, thermal N→N migration of trityl-protected imidazole systems to give the least sterically hindered thermodynamic product. The N→N trityl-migration is difficult to observe by NMR, our efforts to use NOESY and ROESY experiments to track the location of the trityl group proved inconclusive, thus X-ray crystallography has played a key role in this study. The observation of N→N trityl migrations has important implications on account of the extensive use of trityl and trityl-derived groups in imidazole-based medicinal compounds, such as the antifungal agents clotrimazole, fluotrimazole, and bifonazole, as well as in the field of synthetic chemistry.

Ongoing work in our group is aimed at optimizing and extending these domino reaction pathways to develop new, efficient routes to highly complex, natural product-inspired substrates.

Experimental Section

(±)-(5a*S*,8a*S*)-7-Phenyl-1-trityl-5,5a,7,8b-tetrahydroimidazo-[4,5-*e*]isoindole-6,8(7*H*,8a*H*)-dione (2). To 1-trityl-4-vinyl-1*H*-imidazole (**1**) (264 mg, 0.52 mmol) in toluene (10 mL) was added *N*-phenylmaleimide (224 mg, 1.30 mmol) and the solution stirred at reflux for 3 h. The solvent was removed, and the crude residue was chromatographed on silica gel (ethyl acetate−petroleum ether 40/60, 40:60) to yield the title compound as a white solid, 207 mg (78%): R_f 0.42 (UV active, ethyl acetate−petroleum ether 40/60, 40:60); mp 208−211 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.55−7.51 (6H, m), 7.47−7.34 (13H, m), 7.13 (2H, dd, J = 7.0, 1.6 Hz), 5.65 (1H, ddd, J = 5.4, 3.8, 3.8 Hz), 4.37 (1H, ddd, J = 6.0, 3.1, 3.1 Hz), 2.98 (1H, ddd, J = 15.4, 7.8, 1.1 Hz), 2.77 (1H, ddd, J = 8.2, 8.1, 0.7 Hz), 2.00 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 178.0, 174.0, 162.2, 155.5, 142.2, 131.6, 130.4, 129.1, 128.7, 128.1, 127.7, 126.6, 102.2, 75.0, 58.9, 42.0, 36.8, 26.3; IR 2362, 1709, 1381, 1160, 750, 701; HRMS calcd for $C_{34}H_{27}N_3O_2$ (M + Na)$^+$ 532.1995, found 532.2007.

(±)-(5a*S*,8a*S*)-5,5a-Dihydro-7-phenyl-1-tritylimidazo[4,5-*e*]-isoindole-6,8(1*H*,4*H*,7*H*,8a*H*)-dione (3). To 1-trityl-4-vinyl-1*H*-imidazole (**1**) (1.0 g, 2.97 mmol) in toluene (37 mL) was added *N*-phenylmaleimide (1.29 g, 7.43 mmol) and the solution stirred at reflux for 3 h. The reaction mixture was concentrated to a low volume and cooled. The resulting colorless crystals were filtered, yielding the title compound, 80 mg (5%): R_f 0.29 (UV active, methanol−diethyl ether, 2:98); mp 190 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 7.43−7.30 (12H, m), 7.29 (1H, s), 7.17−7.14 (6H, m), 7.09−7.07 (2H, m), 2.56 (1H, ddd, J = 19.2, 4.8, 4.8 Hz), 2.37 (1H, ddd, J = 19.7, 14.6, 5.4 Hz), 2.13 (1H, ddd, J = 12.0, 8.2, 4.2 Hz), 1.53−1.44 (2H, m); ^{13}C NMR, (101 MHz, $CDCl_3$) δ_C 177.7, 173.7, 142.4, 142.2, 142.0, 141.8, 141.0, 130.8, 129.1, 128.5, 128.2, 127.9, 126.4, 77.3, 42.4, 40.8, 24.9, 23.0; IR 2970, 2360, 1716, 1379, 1174, 823, 751, 703; HRMS calcd for $C_{34}H_{27}N_3O_2$ (M + Na)$^+$ 532.1995, found 532.2006. Anal. Calcd for $C_{34}H_{27}N_3O_2$: C, 80.13; H, 5.34; N, 8.25. Found: C, 80.00; H, 5.26; N, 8.20.

(±)-(5a*S*,8a*S*)-5,5a-Dihydro-7-phenyl-3-tritylimidazo[4,5-*e*]-isoindole-6,8(3*H*,4*H*,7*H*,8a*H*)-dione (4). To 1-trityl-4-vinyl-1*H*-imidazole (**1**) (500 mg, 0.98 mmol) in toluene (18.5 mL) was added *N*-phenylmaleimide (425 mg, 2.45 mmol) and the solution

stirred at reflux for 5 h. The solvent was removed, and the crude residue was chromatographed on silica gel (ethyl acetate−petroleum ether 40/60, 60:40) to yield the title compound as a white solid, 240 mg (32%): R_f 0.10 (UV active, methanol−diethyl ether, 2:98); mp >232 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40−7.35 (2H, m), 7.31 (1H, s), 7.27−7.23 (10H, m), 7.15−7.12 (2H, m), 7.05−7.02 (6H, m), 4.21 (1H, d, J = 10.4 Hz), 3.31 (1H, ddd, J = 10.4, 6.0, 6.0 Hz), 2.12−2.06 (1H, m), 1.72 (1H, ddd, J = 19.8, 5.3, 4.8 Hz), 1.67−1.59 (1H, m), 1.43 (1H, ddd, J = 19.6, 12.7, 5.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 177.6, 174.8, 141.5, 139.1, 132.1, 131.6, 129.9, 129.4, 129.1, 128.5, 128.3, 128.2, 126.5, 75.1, 41.5, 40.3, 22.6, 21.0; IR 2962, 2360, 1712, 1380, 1177, 701; HRMS calcd for $C_{34}H_{27}N_3O_2$ $(M + Na)^+$ 532.1995, found 532.2003. Anal. Calcd for $C_{34}H_{27}N_3O_2$: C, 80.13; H, 5.34; N, 8.25. Found: C, 79.96; H, 5.33; N, 8.15.

(±)-(5*S*,5a*S*,8a*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-7-phenyl-3-trityl-5,5a,7,8-tetrahydroimidazo[4,5-*e*]isoindole-6,8-(3*H*,4*H*)-dione (7). To 1-trityl-4-((*E*)-3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-imidazole (**6**) (600 mg, 1.2 mmol) in toluene (28 mL) was added *N*-phenylmaleimide (520 mg, 3.0 mmol) and the solution stirred at reflux for 20 h. The solvent was removed, and the crude residue was chromatographed on silica gel (ethyl acetate−petroleum ether 40/60, 60:40) to yield the title compound as a pale yellow solid, 496 mg (63%): R_f 0.48 (UV active, ethyl acetate−petroleum ether 40/60, 80:20); mp 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42 (2H, ddd, J = 9.6, 9.6, 0.7 Hz), 7.35 (2H, dd, J = 9.3, 0.7 Hz), 7.30−7.27 (9H, m), 7.12 (2H, dd, J = 9.4, 2.2 Hz), 7.09−7.07 (6H, m), 4.27 (1H, d, J = 9.6 Hz), 3.93 (1H, dd, J = 12.5, 7.8 Hz), 3.65 (1H, dd, J = 12.4, 9.9 Hz), 3.50 (1H, dd, J = 9.8, 4.8 Hz), 2.12−2.08 (2H, m), 1.10 (1H, ddd, J = 18.0, 16.0, 1.0 Hz), 0.72 (9H, s), −0.09, −0.17 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 176.1, 174.5, 141.2, 139.1, 132.2, 131.9, 129.7, 129.3, 129.0, 128.4, 128.2, 128.1, 126.4, 75.0, 64.1, 42.8, 41.4, 38.9, 25.8, 23.8, 18., −5.5, −5.6; IR 2925, 2316, 1710, 1384, 1085, 700; HRMS calcd for $C_{41}H_{43}N_3O_3Si$ $(M + H)^+$ 654.3146, found 654.3145. Anal. Calcd for $C_{41}H_{43}N_3O_3Si$: C, 75.31; H, 6.63; N, 6.43. Found: C, 75.21; H, 6.57; N, 6.37.

(±)-((5*S*,5a*S*,8a*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-8a-((*R*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-7-phenyl-3-trityl-5,5a,7,8a-tetrahydroimidazo[4,5-*e*]isoindole-6,8(3*H*,4*H*)-dione (8). (See the Supporting Information for an alternative procedure from **7**.) To 1-trityl-4-((*E*)-3-(*tert*-butyldimethylsilyloxy)prop-1-enyl)-1*H*-imidazole (**6**) (430 mg, 0.9 mmol) in toluene (20 mL) was added *N*-phenylmaleimide (387 mg, 2.2 mmol) and the solution stirred at reflux for 72 h. The solvent was removed, and the crude residue was chromatographed on silica gel (ethyl acetate−petroleum ether 40/60, 5% increasing to 60%) to yield the title compound as a brown solid, 420 mg (57%), and a minor amount of **7**, as a yellow solid, 59 mg (10%): R_f 0.68 (UV active, ethyl acetate−petroleum ether 40/60, 35:65); mp 185−188 °C; ^{1}H NMR, (400 MHz, $CDCl_3$) δ_H 7.39 (6H, ddd, J = 9.6, 8.9, 1.6 Hz), 7.34−7.33 (1H, m), 7.31−7.30 (5H, m), 7.29−7.27 (3H, m), 7.26−7.23 (3H, m), 7.16−7.14 (2H, m), 7.04 (6H, ddd, J = 4.4, 1.6, 1.6 Hz), 4.83 (1H, dd, J = 12.1, 8.9 Hz), 3.93 (1H, dd, J = 12.9, 7.9 Hz), 3.58 (1H, dd, J = 12.6, 9.9 Hz), 3.22 (1H, d, J = 5.1 Hz), 3.11 (1H, dd, J = 23.0, 12.2 Hz,), 2.79 (1H, dd, J = 23.0, 8.9 Hz), 2.13 (1H, dd, J = 20.3, 4.3 Hz), 2.03−1.95 (1H, m), 1.10 (1H, dd, J = 20.3, 15.1 Hz), 0.66 (9H, s), −0.14 and −0.21 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 176.4, 175.3, 174.5, 174.5, 141.2, 139.9, 133.5, 132.0, 131.5, 131.0, 129.7, 129.3, 129.1, 128.9, 128.7, 128.5, 128.3, 126.8, 126.4, 75.3, 63.9, 49.3, 44.8, 44.2, 40.6, 32.0, 25.9, 24.1, 18.2, −5.3 and −5.4; IR 2325, 1781, 1711, 1498, 1378, 1185, 1089, 837, 747, 700; HRMS calcd for $C_{51}H_{50}N_4O_5Si$ $(M + Na)^+$ 849.3443, found 849.3450.

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Supporting Information Available: Experimental procedures for the synthesis of **1** and **6**. ^{1}H, ^{13}C spectra for compounds **1**−**4** and **6**−**8**. Crystallographic information files (CIFs) for compounds **1**, **3**, **4**, **7**, and **8**. Experimental details, optimized atomic coordinates, and final energies for Hartree−Fock model of **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.