Synthesis of Some Unsymmetrical Bridged Terpyridines

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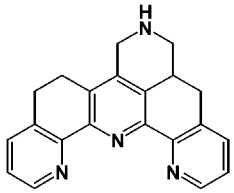
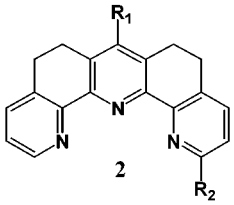
Novel unsymmetrical terpyridines **1** and **2** are synthesized using *intra*- and *inter*molecular Michael additions as the key reactions, followed by the construction of the central pyridine ring. Terpyridine **1** represents a heretofore unknown hexacyclic ring system.

Fused pyridines are useful substructures in the design of supramolecular compounds, and 2,2′-bipyridine (bpy) and its bridged analogues are especially valuable ligands.[1] Over the past 3 decades there has been a significant effort to develop even tighter binding ligands by fusing rings to bpy and/or extending the polyaza cavity. Among other closely related ligands, 2,2′:6′,2″-terpyridine (tpy) and its bridged analogues have been found to be very effective tridentate chelating systems.[2] They have been shown to bind tightly to a variety of metals and are now finding their way into investigations of luminescence and molecular electronics.[3]

In the course of other studies,[4] we needed the unsymmetrical bridged terpyridines **1** and **2**. Simple unbridged terpyridines and their complexes have been known since the 1930s.[5] Bridged terpyridines, however, were first reported less than 2 decades ago, and virtually[6] all that have been synthesized to date are symmetrical.[7] We now report a route for the synthesis of unsymmetrical members of this family, as well as the first synthesis of any member of the pyrido[3,4,5-*de*]quino[8,7-*b*][1,10] phenanthroline ring system present in **1**. The extension of the



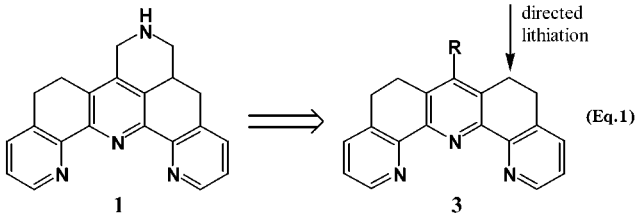
1



2

reported methodology may become useful in the preparation of unsymmetrical polyheterocyclic compounds, in the introduction of bridging to control conformations, and the improvement of solubility by providing a means for installing peripheral solubilizing substituents.

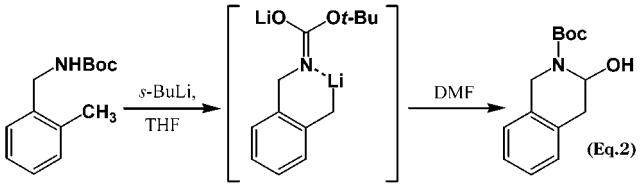
Synthesis of Hexacycle 1. The existence in the literature of a highly convergent route[7c] to some symmetrical bridged U-shaped terpyridines (e.g., **3**) suggested that **1** might be most easily accessed by a strategy (eq 1)



1 **3** (Eq.1)

U-Shaped Terpyridine

involving lateral lithiation of **3**, where R is a directing group for lateral lithiation.[8] One good precedent[9] for achieving a similar transformation on a simpler substrate is shown in eq 2; removal of the hydroxyl and Boc groups en route to **1** was expected to be straightforward.



(Eq.2)

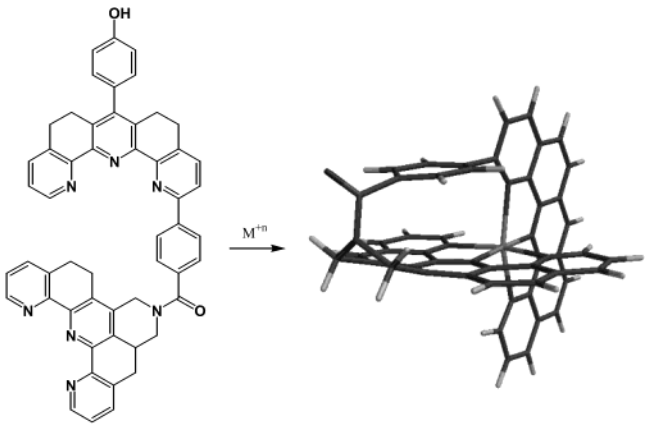
83%

(1) Constable, E. C. *Metals and Ligand Reactivity*; VCH Publishers: New York, 1996.

(2) Thummel, R. P. *Tetrahedron* **1991**, *47*, 6851.

(3) (a) Mallet, C.; Thummel, R. P.; Hery, C. *Inorg. Chim. Acta* **1993**, *210* (2), 223. (b) Hissler, M.; El-ghayoury, A.; Harriman, A.; Ziessel, R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1717.

(4) Compounds **1** and **2** were prepared in the context of a project where we sought to examine the concept of using ground-state destabilization rather than transition state stabilization to achieve rate acceleration. In particular, we sought to use metal ion binding of **i** [or a polymer-bound-analogue (to suppress polymerization)], which was made by coupling of **1** and **2** (in the form of **34**) to twist the amide bond out of resonance (**ii**, phenol linker is omitted for clarity). To date, we have been unable to demonstrate that metal ion binding achieves the desired objective, but we believe that the syntheses of **1** and **2** are of interest in their own right.



i **ii**

(5) Moran, G. T.; Burstall, F. H. *J. Chem. Soc.* **1932**, 20.

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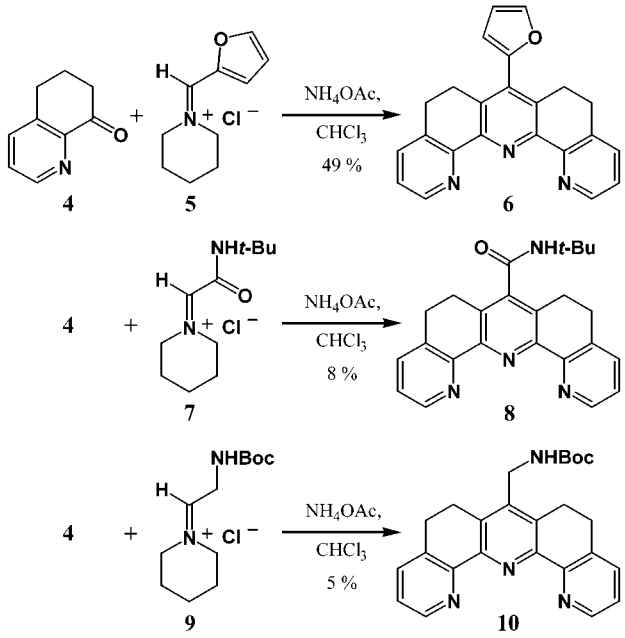
Published on Web 03/13/2002

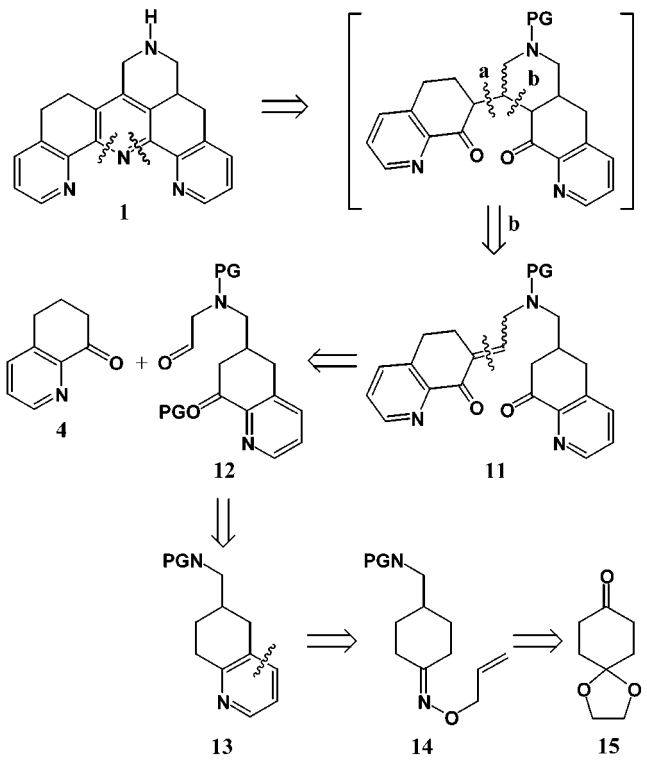
Scheme 1



With the aim of implementing the strategy in eq 1, the known furan **6**[7g] was prepared using a modification[10] of the literature procedure[11] (Scheme 1). There are several functional groups that can serve as directing groups for lateral lithiation, among which are *N*-*tert*-butyl amides and Boc-protected amines.[8] Precedent notwithstanding,[12] conversion of the furan ring of **6** into the *N*-*tert*-butyl amide group of **8**[7g] turned out to be difficult,[10] possibly because of facile decarboxylation of the intermediate acid. Therefore, amide **8** and Boc-protected amine **10** were prepared using the route shown in Scheme 1, substituting **7** and **9** for **5**, respectively.

Compounds **8** and **10** were subjected to lateral lithiation conditions.[8] Use of different bases (*n*-BuLi, *s*-BuLi, *t*-BuLi, LDA), various solvents, and a range of temperatures failed to give any positive results. In the case of amide **8**, only some amide nitrogen methylation was observed when the reaction was quenched with CH_3I.

Scheme 2



At that point it was thought that perhaps the nitrogens' lone pairs (on the pyridines of the ligand) interfere with lateral lithiation, and if they could somehow temporarily be "tied up", then the desired lithiation might be achieved. This strategy was examined using $ZnCl_2$.[13] Unfortunately, as before, no lateral lithiation was observed.

Because of low yields and various misfortunes with lateral lithiation, new approaches toward amine **1** were considered. It was decided that, if one could not do chemistry on the pentacyclic ligands in order to build the sixth ring, then formation of the hexacyclic skeleton from considerably less complex precursors needed to occur at a very late stage. This new strategy would probably lead to a longer synthesis, since amine **1** is not symmetrical, but it would be based on a more certain synthetic route.

The retrosynthesis was therefore changed to that outlined in Scheme 2. Amine **1** was disconnected at the central pyridine ring, which can be constructed from a 1,5-diketone. One further disconnection, a retro-*inter*molecular Michael addition (disconnection a) was explored first but proved to be unsuccessful due to the instability of the corresponding α,β-unsaturated ketone.[14] However, it was thought that an *intra*molecular Michael addition (route b) involving an enedione of type **11** could also provide access to the desired system. Further disconnection of enedione **11** affords two pieces: the quinolone **4**, which was used previously,[10] and keto aldehyde **12** (or a protected form of it). Compound **12** might be assembled from a 6-substituted tetrahydroquinoline (**13**). The pyridine ring of tetrahydroquinoline **13** theoretically can

(6) The only exceptions to that statement were prepared by degradation of more complex systems. See: (a) Bell, T. W.; Hou, Z.; Zimmerman, S. C.; Thiessen, P. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2163. (b) Bell, T. W.; Hou, Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1536.

(7) (a) Thummel, R. P.; Jahng, Y. *J. Org. Chem.* **1985**, *50*, 2407. (b) Thummel, R. P.; Jahng, Y. *Inorg. Chem.* **1986**, *25*, 2527. (c) Hegde, V.; Jahng, Y.; Thummel, R. P. *Tetrahedron Lett.* **1987**, *28*, 4023. (d) Thummel, R. P. *Synlett* **1992**, 1. (e) Hung, C.-Y.; Wang, T.-L.; Shi, Z.; Thummel, R. P. *Tetrahedron* **1994**, *50*, 10685. (f) Mallet, C.; Thummel, R. P.; Hery, C. *Inorg. Chim. Acta* **1993**, *210*, 223. (g) Hung, C.-Y.; Wang, T.-L.; Jang, Y.; Kim, W. Y.; Schmehl, R. H.; Thummel, R. P. *Inorg. Chem.* **1996**, *35*, 5953. Ligands **6** and **8** can be fully aromatized into **6a** and **8a**, respectively, using Pd/C and nitrobenzene (see the Supporting Information). Besides acting as a polar, high-boiling solvent, nitrobenzene permits a disproportionation to occur, providing the fully aromatic ligand in a good yield along with a corresponding amount of aniline. (h) Riesgo, E. C.; Jin, X.; Thummel, R. P. *J. Org. Chem.* **1996**, *61*, 3017. (i) Jahng, Y.; Thummel, R. P.; Bott, S. G. *Inorg. Chem.* **1997**, *36*, 3133.

(8) For reviews, see: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. In *Advances in Heterocyclic Chemistry*; Academic Press: New York, 1991; Vol 52, pp 187−303. (c) Clark, R. D.; Jahangir, A. In *Organic Reactions*; Paquette, L. A., Ed; Wiley: New York, 1995; Vol 47, Ch.1, pp 1−314.

(9) Clark, R. D.; Jahangir; Langston, J. A. *Can. J. Chem.* **1994**, *72*, 23.

(10) See the Supporting Information.

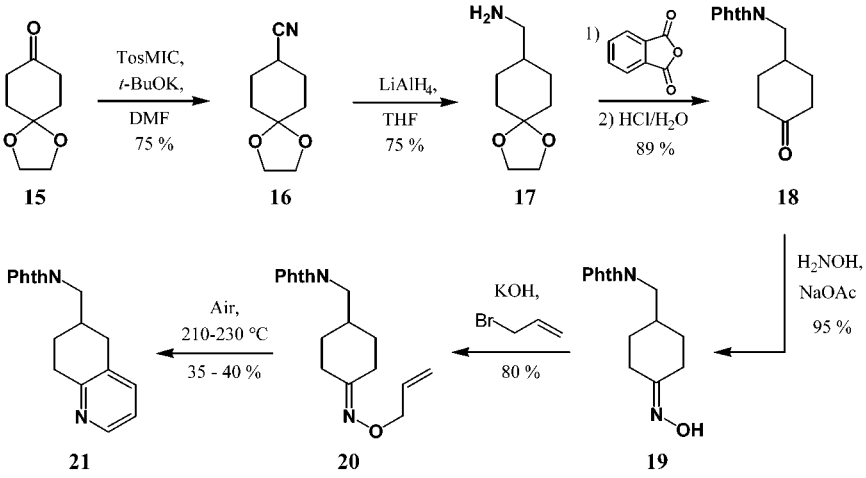
(11) Keuper, R.; Risch, N.; Flörke, U.; Haupt, H.-J. *Liebigs Ann.* **1996**, 705.

(12) For conversion of furans into carboxylic acids, see: (a) Piancatelli, G.; D'Auria, M.; D'Onofrio, F. *Synthesis* **1994**, 867. (b) Yamazaki, T.; Mizutani, K.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 4346. (c) Dondoni, A.; Marra, A.; Scherrmann, M.-C. *Tetrahedron Lett.* **1993**, *34*, 7323.

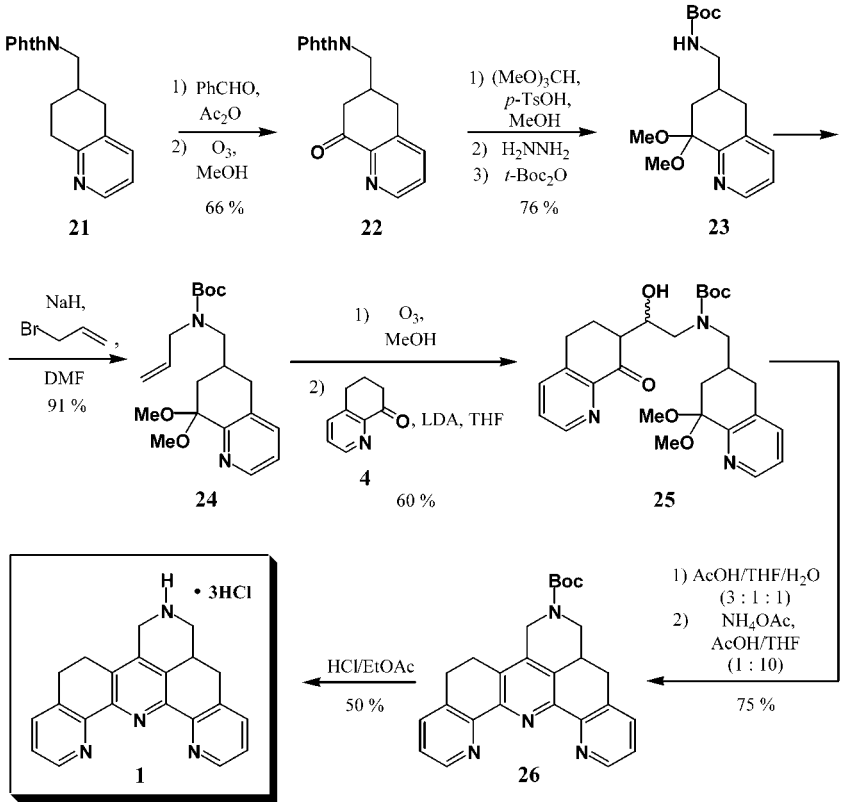
(13) A dramatic R_f difference of the complex vs the metal-free substrate was observed by TLC; the complex can be easily destroyed by washing with EDTA.

(14) Lebedev, R. L.; Kelly, T. R. Unpublished results.

Scheme 3



Scheme 4



be made by thermolysis[15] of the oxime *O*-allyl ether **14**, which in turn might be constructed from commercially available monoprotected cyclohexanedione **15**.

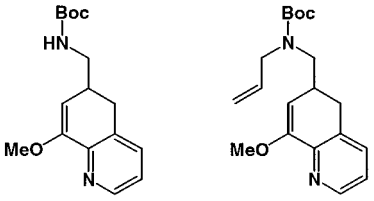
The first goal was to prepare the 6-substituted tetrahydroquinoline **13**. Using thermolysis of an oxime *O*-allyl ether, Kakisawa and Irie and their co-workers prepared unsubstituted 5,6,7,8-tetrahydroquinoline.[15] The proposed mechanism of this unusual reaction is described in the literature.[15] It is thought that the oxime *O*-allyl ether, when heated neat to ~180 °C, undergoes a [2,3]-sigmatropic rearrangement before reacting with oxygen in the air.

To test if the thermolysis would work on a more complex substrate like **14**, primary amine **17** was prepared according to the procedure of Becker[16] (Scheme 3). The thermally stable phthalimide protecting group was chosen, since in order to effect thermolysis it would be necessary to heat the *O*-allyl ether to ~180 °C. Acid-catalyzed hydrolysis of the ketal then afforded ketone **18**, which was converted into oxime **19** using hydroxylamine hydrochloride. The reaction of **19** with KOH and allyl bromide afforded *O*-allyl ether **20**. Finally, overnight thermolysis at 210−230 °C in air afforded 6-substituted quinoline **21**. The temperature had to be higher than described in the literature[15] and properly maintained in order to achieve a 35−40% yield of the product (**21**).

We were delighted to see that this relatively unexplored method of making the pyridine ring of tetrahydroquinoline itself also worked on a more complex substrate like **20**. It is worth noting that this seven-step synthesis of **21** involves only one column chromatography purification (compound **21**) and can be done on a large scale.

Compound **21** was laterally olefinated and ozonized to afford quinolone **22** (Scheme 4). Ketone **22** was then converted into its dimethyl acetal, the phthalimide was

removed, and the Boc protecting group was installed, affording urethane **23**. During the process, MeOH elimination afforded some of the corresponding enol ether **23a**.



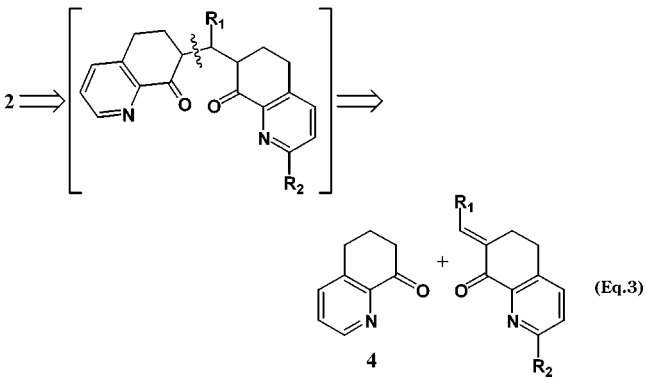
23a **24a**

These urethanes were produced as a 2:1 mixture of compounds **23**/**23a**. Attachment of the allyl chain proceeded smoothly using the mixture of urethanes and produced a 2:1 mixture of compounds **24**/**24a**. Ozonolysis of the terminal olefin produced an aldehyde, which was then reacted with the lithium enolate of **4** (prepared according to Chelucci[17]), affording the unstable alcohol **25**.

Deprotection of the dimethyl acetal in **25** according to Corey's procedure[18] did not simply produce the desired ketone but instead produced a complex (as judged by TLC and NMR) mixture that was closed into the new hexacyclic ring system, **26**, on treatment with NH_4OAc. The unknown mixture is unstable; therefore, it was very important to use mild conditions for the reaction, namely a 1:10 mixture of AcOH:THF, instead of the usual[19] neat AcOH. After optimization, ligand **26** was produced in 75% yield from the alcohol **25**. When working on a relatively large scale, it is preferable to convert **24** directly to **26** (41% overall) without purification of **25**.

With **26** in hand, what was left was to remove the Boc protecting group. This proved to be more difficult than expected, possibly because of the adverse instability of **26**, but the amine **1** was eventually produced as its tri-HCl salt in 50% yield.

Synthesis of 2. The retrosynthesis (eq 3) was based on knowledge acquired in the preceding studies. As was



(Eq.3)

done previously for **1**, **2** was retrosynthetically cleaved at the central pyridine ring, which can be constructed from a 1,5-diketone. The key disconnection (retro-*inter*molecular Michael addition) affords two pieces: the quinolone **4**, and an α,β-unsaturated ketone.

The synthesis of compounds **2** is described in Scheme 5. Stille[20] coupling between acid chloride **27** and tributyl(vinyl)tin afforded the unstable and heat-sensitive α,β-unsaturated ketone **28** in 60% yield. Mukaiyama[21] addition, which required stoichiometric (not just catalytic) amounts of $SnCl_2$ and TMSCl, provided the 1,5-diketone **29**, which was then cyclized into tetrahydroquinoline **30**. Lateral olefination and ozonolysis afforded quinolone **31**.

Quinolone **31** was then condensed with *p*-benzyloxybenzaldehyde to produce α,β-unsaturated ketone **32** as a bright yellow solid. Intermolecular Michael addition proceeded smoothly, affording the 1,5-diketone first, which was closed into the pyridine ring to generate **33**. One can envisage this route being used as a general approach to type **2** molecules by introducing various R_1 and R_2 groups. For our purposes,[4] we needed a carboxylic acid functional group for coupling with amine **1**. Therefore, **33** was treated with aqueous acid (nitrile hydrolysis and benzyl deprotection occurred at the same time) to produce acid **34** as a mixture of mono- and di-HCl salts.

In conclusion, the syntheses of unsymmetrical ligands **1** and **2** have been achieved using intra- and intermolecular Michael reactions as the key steps, followed by the construction of the central pyridine ring. Both approaches should be useful for accessing a range of unsymmetrical bridged terpyridines with various functional groups.

Experimental Section

General. Anhydrous THF and anhydrous ethyl ether were obtained by distillation under nitrogen from sodium and benzophenone. Anhydrous CH_2Cl_2 was obtained by distillation under nitrogen from calcium hydride. Other anhydrous solvents were purchased from Aldrich in Sure/Seal bottles. Butyllithiums were usually titrated prior to use. Analytical TLC was conducted on Whatman 0.25 mm polyester-backed PE SIL G/UV silica plates, EM Science aluminum oxide $60F_{254}$ neutral (aluminum sheets) 0.2 mm alumina plates, or Selecto Scientific (Suwanee, GA) Alumina B, F-254, 0.2 mm basic alumina plates. Preparative TLC was conducted on silica gel GF preparative Uniplates (Analtech), alumina (neutral) GF preparative Uniplates (Analtech), or ALOX-100 UV_{254} basic alumina plates (Macherey-Nagel). Other specific preparative TLC plates are indicated in the individual procedures. Preparative TLC plates were usually extracted with MeOH or a 1:1 $MeOH/CH_2Cl_2$ mixture unless otherwise indicated. Flash column chromatography was conducted using silica gel purchased from Fisher Scientific (Davisil Type 60 Å Grade 1740 170−400 mesh) and basic alumina, activated, Brockmann I purchased from Aldrich (~150 mesh, 58 Å). Low- and high-resolution mass spectra were determined by Boston University or University of Illinois at Urbana−Champaign Mass Spectrometry Laboratories. Elemental analyses were performed by Robertson Microlit Laboratory, Inc., Madison, NJ. Ozonolysis reactions were always tested for peroxides with EM Quant Peroxide Test paper (EM Science) before workup. House vacuum varied between 30 and 70 Torr and high vacuum varied between 0.1 and 0.2 Torr.

2-[(4-Oxocyclohexyl)methyl]isoindoline-1,3-dione (18). Amine **17** (10.0 g, 54.5 mmol), prepared in two steps (75% each) from 1,4-cyclohexanedione monoethylene acetal according to

(15) (a) Kusumi, T.; Yoneda, K.; Kakisawa, H. *Synthesis* **1979**, 221. (b) Irie, H.; Katayama, I.; Mizuno, Y.; Koyama, J.; Suzuta, Y. *Heterocycles* **1979**, *12*, 771. (c) Koyama, J.; Sugita, T.; Suzuta, Y.; Irie, H. *Chem. Pharm. Bull.* **1983**, *31*, 2601.

(16) Becker, D. P.; Flynn, D. L. *Synthesis* **1992**, 1080. For the mechanism of the TosMIC reaction, see: Oldenziel, O. H.; van Leusen, D.; van Leusen, A. M. *J. Org. Chem.* **1977**, *42*, 3114.

(17) Chelucci, G.; Saba, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2575.

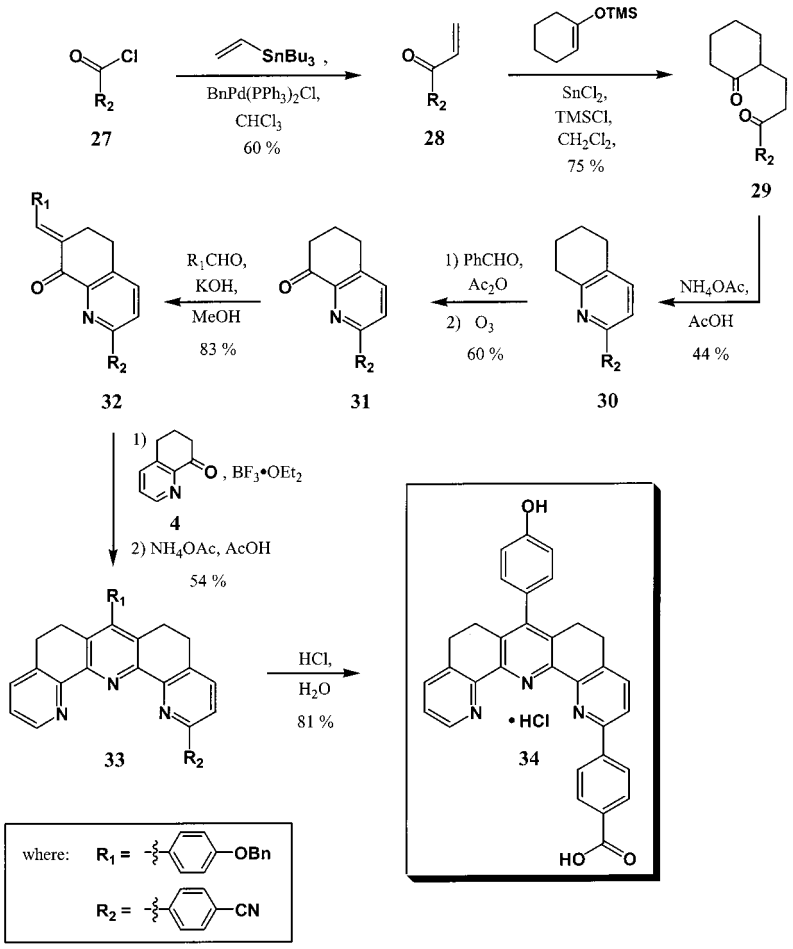
(18) Corey, E. J.; Nicolaou, K. C.; Toru, T. *J. Am. Chem. Soc.* **1975**, *97*, 2287.

(19) Constable, E. C.; Harverson, P.; Smith, D. R.; Whall, L. A. *Tetrahedron* **1994**, *50*, 7799.

(20) (a) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129. (b) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634.

(21) Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1987**, 463.

Scheme 5



the procedure of Becker,[16] and phthalic anhydride (8.66 g, 54.5 mmol) were placed in a 200 mL pear-shaped pressure flask with a threaded seal. The flask was sealed and heated (behind a safety shield) in an oil bath at ~135 °C with stirring for ~30 min. The flask was then allowed to cool to room temperature and cautiously opened, and 20 mL of 1 M HCl was added. The flask was resealed and heated (behind a safety shield) in an oil bath at ~135 °C with vigorous stirring for ~2 h. After this period it was then allowed to cool to room temperature and cautiously opened, and 200 mL of CH_2Cl_2 was added. The organic layer was collected, washed with 1 M HCl, dried over Na_2SO_4, and then concentrated in vacuo to afford ketone **18** as an off-white solid (13.4 g, 89%), which was normally used for the next reaction without further purification. An analytical sample was obtained after crystallization from ether as a white solid: mp 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46−1.56 (m, 2H), 1.99−2.04 (m, 2H), 2.23−2.42 (m, 5H,), 3.64 (d, 2H, J = 7.2 Hz), 7.71 (dd, 2H, J = 5.4, 3.2 Hz), 7.83 (dd, 2H, J = 5.4, 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4, 35.7, 40.3, 42.6, 123.4, 131.9, 134.1, 168.4, 210.8; IR ($CDCl_3$) ν 1774, 1712 cm^{-1}. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.90; H, 5.68; N, 5.66.

2-{[4-(Hydroxyimino)cyclohexyl]methyl}isoindoline-1,3-dione (19). Ketone **18** (9.07 g, 35.3 mmol), hydroxylamine hydrochloride (4.90 g, 70.6 mmol), and sodium acetate trihydrate (9.60 g, 70.6 mmol) were placed in a 1 L round-bottomed flask equipped with a condenser. Water (160 mL) and MeOH (~400 mL, enough to effect a complete dissolution) were added, and the solution was heated in an oil bath at ~70 °C with stirring overnight. Most of the MeOH was then removed in vacuo (rotary evaporator) and the remaining material was extracted with ether (3 × 100 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution twice and with saturated NaCl solution once. The organic layer was then dried over Na_2SO_4 and concentrated in vacuo to afford oxime **19** as a white solid (9.10 g, 95%), which was used for the next reaction without further purification: mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17−1.32 (m, 2H), 1.72−1.87 (m, 3H), 2.01−2.09 (m, 2H,), 2.41 (d, 1H, J = 14.6 Hz), 3.27 (d, 1H, J = 14.6 Hz), 3.58 (d, 2H, J = 6.8 Hz), 7.70 (dd, 2H, J = 5.4, 3.2 Hz), 7.83 (dd, 2H, J = 5.4, 3.2 Hz), 9.05 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 29.4, 30.6, 31.0, 36.6, 43.1, 123.3, 131.9, 134.0, 159.5, 168.5; IR ($CDCl_3$) ν 3455 (br), 3235 (br), 1773, 1707 cm^{-1}. Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.09; H, 5.84; N, 10.40.

2-{[4-(Prop-2-enyloxyimino)cyclohexyl]methyl}isoindoline-1,3-dione (20). Oxime **19** (10.0 g, 36.8 mmol), anhydrous DMF (150 mL), and allyl bromide (16.0 mL, 184 mmol) were placed in a 500 mL round-bottomed flask under argon. The reaction flask was then cooled in ice, and 3.15 g (ca. 48 mmol) of 85% KOH pellets crushed into a fine powder was added all at once. The reaction flask was then heated in an oil bath at ~40 °C for 3 h with vigorous stirring. After this period, the reaction mixture was poured into 500 mL of water and the resulting mixture was extracted with hexanes (3 × 200 mL). The combined extracts were washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo to afford 8.03 g (70%; note: yields on a 1 g scale are usually ~80%) of *O*-allyl ether **20** as a yellowish oil, which was used for the next reaction without further purification. The oil usually crystallizes in several days into a beige-yellow solid: mp 47−49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12−1.28 (m, 2H), 1.68−1.86 (m, 3H), 1.94−2.04 (m, 2H), 2.36 (d, 1H, J = 14.0 Hz), 3.19 (d, 1H, J = 14.0 Hz), 3.53 (d, 2H, J = 6.8 Hz), 4.44 (d, 2H, J = 4.0 Hz), 5.12 (d, 1H, J = 10.4 Hz), 5.20 (d, 1H, J = 17.2 Hz), 5.86−5.96 (m, 1H), 7.66 (dd, 2H, J = 5.4, 3.2 Hz), 7.78 (dd, 2H, J = 5.4, 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 29.5, 30.6, 30.9, 36.5, 43.0, 74.1, 116.9, 123.2, 131.8, 133.9, 134.5, 158.9, 168.3; IR ($CDCl_3$) ν 1774, 1713 cm^{-1}. Anal. Calcd

for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.26; H, 6.53; N, 8.60.

2-[[6-(5,6,7,8-Tetrahydroquinolyl)]methyl]isoindoline-1,3-dione (21). *O*-Allyl ether **20** (25.0 g, 0.077 mol) was placed in a 100 mL round-bottomed flask equipped with a short condenser. The reaction was stirred and heated in a sand bath for 18−21 h. The reaction was carried out open to the air. The temperature was measured by inserting the thermometer into the sand touching the bottom quarter of the flask (important: the temperature must be between 210 and 230 °C). The reaction was then cooled, and the resulting dark brown oil was dissolved in $CHCl_3$ and adsorbed on silica (∼50 g). Flash column chromatography using a 8 × 25 cm silica column and eluting with 80:20 EtOAc/hexanes afforded compound **21** (8.19 g, 35%) as a very hard beige solid: mp 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52−1.62 (m, 1H), 2.00−2.05 (m, 1H), 2.22−2.30 (m, 1H), 2.52−2.59 (m, 1H), 2.75−3.04 (m, 3H), 3.70 (d, 2H, J = 6.8 Hz), 6.97 (dd, 1H, J = 7.8, 4.6 Hz), 7.28 (d, 1H, J = 7.8 Hz), 7.69 (dd, 2H, J = 5.4, 3.2 Hz), 7.82 (dd, 2H, J = 5.4, 3.2 Hz), 8.30 (d, 1H, J = 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 31.9, 33.2, 33.9, 43.2, 121.0, 123.3, 130.4, 131.9, 134.0, 136.8, 147.1, 156.5, 168.5; IR ($CDCl_3$) ν 1774, 1713 cm^{-1}. Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 73.61; H, 5.53; N, 9.23.

2-[[6-(8-Oxo-5,6,7-trihydroquinolyl)]methyl]isoindoline-1,3-dione (22). Compound **21** (2.77 g, 9.47 mmol), benzaldehyde (2.88 mL, 28.4 mmol), and acetic anhydride (3.57 mL, 37.9 mmol) were placed together into a 25 mL round-bottomed flask fitted with a condenser and the reaction was refluxed with stirring under argon overnight (temperature of the oil bath was ∼160 °C). The resulting brown liquid was diluted with CH_2Cl_2 (50 mL) and water (150 mL), the aqueous phase was made strongly basic with 2 M NaOH, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL); the combined CH_2Cl_2 layer and extracts were dried over Na_2SO_4 and concentrated in vacuo, affording the crude benzylidene olefin as a brown liquid, which contains some unreacted starting material and substantial amounts of benzaldehyde. The crude olefin was then dissolved in anhydrous CH_2Cl_2 (60 mL) and anhydrous MeOH (40 mL). Ozone generated using an Osmonics system set at 1 amp with an oxygen flow rate of 2 L/min was bubbled through at ca. −40 °C with stirring for ∼30 min (until disappearance of the starting material as judged by silica TLC eluting with 90:10 hexanes/EtOAc). The reaction mixture was then purged with argon for ∼5 min and quenched with 10 mL of anhydrous dimethyl sulfide. The reaction was then allowed slowly to warm to room temperature and left to stir overnight under argon. Solvents were then partially removed and the reaction was adsorbed on silica (∼15 g). Flash column chromatography using a 5 × 15 cm column and eluting with 80:20 EtOAc/hexane and then pure EtOAc afforded ketone **22** (2.07 g, 71%) as a white solid: mp 201−203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (dd, 1H, J = 16.4, 12.4 Hz), 2.70−2.75 (m, 1H), 2.86−3.03 (m, 3H), 3.76 (d, 2H, J = 6.8 Hz), 7.35 (dd, 1H, J = 7.8, 4.6 Hz), 7.61 (d, 1H, J = 7.8 Hz), 7.71 (dd, 2H, J = 5.4, 3.2 Hz), 7.81 (dd, 2H, J = 5.4, 3.2 Hz), 8.65 (d, 1H, J = 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.3, 34.1, 42.1, 43.6, 123.4, 127.2, 131.7, 134.2, 137.8, 138.8, 147.7, 149.4, 168.2, 195.0; IR ($CDCl_3$) ν 1773, 1712 cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.65; H, 4.60; N, 8.97.

6-[*N*-(*tert*-Butyloxycarbonylamino)methyl]-8,8-dimethoxy-5,6,7,8-tetrahydroquinoline (23). Ketone **22** (2.07 g, 6.76 mmol), *p*-toluenesulfonic acid monohydrate (1.29 g, 6.76 mmol), anhydrous trimethyl orthoformate (20 mL), and anhydrous MeOH (150 mL) were placed together under argon into a 250 mL round-bottomed flask and heated at reflux for ∼3 h with stirring. The reaction was mixed with 150 mL of saturated $NaHCO_3$ solution (**CAUTION**: foaming) and then extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with 150 mL of saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated in vacuo affording 2.56 g of dimethyl ketal as a dark yellow oil, which contained small amounts of trimethyl orthoformate. The crude oil was combined with anhydrous EtOH (150 mL) and anhydrous H_2NNH_2 (2.10 mL, 67.6 mmol) and was heated at reflux with stirring under argon overnight. Solvent was then removed in vacuo, 300 mL of water and five pellets of NaOH were added, the solution was saturated with solid NaCl and extracted with CH_2Cl_2 (3 × 100 mL). The extracts were washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo, affording 1.23 g (∼5.5 mmol) of crude primary amine as a yellow oil. The crude oil was then dissolved in 120 mL of anhydrous THF and a 1.0 M solution of di-*tert*-butyl dicarbonate in THF (5.83 mL, 5.8 mmol, Aldrich) was added. The reaction was stirred under argon overnight. Solvent was then removed in vacuo and the residual oil was purified by flash column chromatography using a 5 × 20 cm silica column and eluting with EtOAc. The resulting light yellow oil (1.66 g, 76%) is a 2:1 mixture of compounds **23** and **23a**, which was used for the next reaction without separation: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) are too complex to tabulate.[10] HRMS (FAB) calcd for $C_{17}H_{27}N_2O_4$ (**23**, MH^+) 323.1971, found 323.1971; calcd for $C_{16}H_{23}N_2O_3$ (**23a**, MH^+) 291.1709, found 291.1707.

6-[*N*-(Allyl-*tert*-butyloxycarbonylamino)methyl]-8,8-dimethoxy-5,6,7,8-tetrahydroquinoline (24). The preceding mixture of compounds **23** and **23a** (1.66 g, ca. 5.15 mmol) was placed into a three-necked 100 mL round-bottomed flask and 58 mL of anhydrous DMF was added under argon. The solution was cooled on ice and 95% dry NaH (261 mg, 10.3 mmol) was added slowly over ∼35 min from a solid-addition pear flask under argon. The reaction mixture was vigorously stirred on ice for ∼1 h and then allyl bromide (2.24 mL, 25.8 mmol) was added dropwise over ∼5−10 min. The reaction was stirred for ∼1 h on ice, then opened to the air, and several milliliters of water was added dropwise until the excess of NaH (**CAUTION**: generation of hydrogen!) had reacted. The reaction mixture was then poured into 200 mL of water and the mixture was extracted with hexanes (3 × 100 mL). The extracts were dried over Na_2SO_4 and concentrated in vacuo, affording 1.37 g of crude yellow oil, which was purified by flash column chromatography using a 5 × 15 cm silica column eluting with EtOAc. The resulting light yellow oil (1.38 g, 74%; the yield is scale dependent and is up to 90% on a smaller scale) is a 2:1 mixture of compounds **24** and **24a**, which was used for the next reaction without separation: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) are too complex to tabulate (see Supporting Information). HRMS (FAB) calcd for $C_{20}H_{31}N_2O_4$ (**24**, MH^+) 363.2284, found 363.2283; calcd for $C_{19}H_{27}N_2O_3$ (**24a**, MH^+) 331.2022, found 331.2022.

***tert*-Butoxy-*N*-[[6-(8,8-dimethoxy-5,6,7,8-tetrahydroquinolyl)]methyl]-*N*-[2-hydroxy-2-[7-(8-oxo-5,6,7-trihydroquinolyl)]ethyl]carboxamide (25).** A ∼2:1 mixture of compounds **24** and **24a** (290 mg, ∼0.80 mmol) and 20 mL of anhydrous MeOH were placed into a 50 mL round-bottomed flask. Ozone generated using the Osmonics system set at 1 amp with an oxygen flow rate of 2 L/min was bubbled through at ca. −40 °C with stirring for ∼10 min (until disappearance of the starting material as judged by TLC on silica eluting with EtOAc). The reaction was purged with argon for ∼5 min and quenched with 5 mL of dimethyl sulfide. The reaction was slowly warmed to room temperature and left to stir under argon overnight. Solvent was then removed in vacuo and the crude unstable aldehyde was kept under high vacuum for ∼2 h. The aldehyde was then dissolved in 10 mL of anhydrous THF and added dropwise (over ∼15 min) to a solution of quinolone **4** Li anion at −78 °C (the flask that had contained the aldehyde was washed with an additional 3 mL of anhydrous THF). Quinolone **4** Li anion was prepared according to the procedure of Chelucci:[18] quinolone **4**[10] (141 mg, 0.960 mmol) was dissolved in 20 mL of anhydrous THF under argon and cooled to −78 °C, and a 2.0 M LDA solution in THF (0.500 mL, 1.0 mmol) was added dropwise over 2−3 min; the resulting mixture was stirred at −78 °C for at least 2 h. After addition of aldehyde, the reaction was stirred at −78 °C for ∼15 min and then slowly (∼30 min) warmed to 0 °C and stirred at 0 °C for ∼1 h. The reaction was then quenched at 0 °C with saturated NH_4Cl solution (∼30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over Na_2-

SO_4 and concentrated in vacuo, affording 0.392 g of a beige foam. The foam was purified by preparative TLC (three 1000 μm 20 × 20 cm silica plates, eluting with 95:5 CH_2Cl_2/MeOH), affording unstable compound **25** (242 mg, 60%) as a yellow glass: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) are too complex to tabulate,[10] because **25** is apparently a mixture of stereoisomers; IR ($CDCl_3$) ν 3405 (br), 1690 cm^{-1}; HRMS (FAB) calcd for $C_{28}H_{37}N_3O_6Na$ (MNa^+) 534.2580, found 534.2581.

8-*tert*-Butoxycarbonyl-6,7,8,9,9a,10-hexahydro-5*H*-pyrido[3,4,5-de]quino[8,7-*b*][1,10]phenanthroline (26). Method A. Compound **25** (168 mg, 0.330 mmol) and 20 mL of a 3:1:1 mixture of AcOH/THF/H_2O were stirred together at ∼50 °C for ∼3 h. The reaction was cooled on ice, made strongly basic with 20% NaOH solution, and extracted with CH_2Cl_2 (3 × 20 mL). The extracts were combined, dried over Na_2SO_4, and concentrated in vacuo, affording 136 mg of purple foam. The foam (136 mg), ammonium acetate (468 mg, 6.1 mmol, Aldrich, 99.99+%), 30 mL of anhydrous THF, and 3 mL of glacial acetic acid were refluxed together with stirring under air for ∼3 h. The reaction was then cooled on ice and made strongly basic with 2 M NaOH solution; the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layer and extracts were dried over Na_2SO_4 and concentrated in vacuo, affording 132 mg of yellow oil. Flash column chromatography using a 4 × 15 cm basic alumina column and eluting starting with 80:20 CH_2Cl_2/EtOAc, then with a small amount of 99:1 CH_2Cl_2/MeOH, and finally with 98:2 CH_2Cl_2/MeOH (until the product comes out) afforded compound **26** (105 mg, 75%) as a yellow oil.

Method B. Compound **25** is difficult to prepare on a large scale due to tedious preparative TLC purification and instability. Therefore, compound **26** can be prepared on a larger scale directly from compound **24** according to the following procedure. A ∼2:1 mixture of compounds **24** and **24a** (0.650 g, ∼1.8 mmol) and 30 mL of anhydrous MeOH were placed into a 100 mL round-bottomed flask. Ozone generated using the Osmonics system set at 1 amp with an oxygen flow rate of 2 L/min was bubbled through at ca. −40 °C with stirring for ∼15 min (until disappearance of the starting material by TLC eluting with EtOAc). The reaction was then purged with argon for ∼5 min and quenched with 5 mL of dimethyl sulfide. The reaction was then allowed to warm slowly to room temperature and left to stir under argon overnight. Solvent was then removed in vacuo and crude unstable aldehyde was further kept under high vacuum for 1−2 h. The aldehyde was then dissolved in 20 mL of anhydrous THF and added dropwise (over ∼20 min) to the solution of quinolone **4** Li anion at −78 °C (the flask was washed with an additional 5 mL of anhydrous THF). Quinolone **4** Li anion was prepared according to the procedure of Chelucci:[17] quinolone **4**[10] (317 mg, 2.16 mmol) was dissolved in 30 mL of anhydrous THF under argon and cooled to −78 °C, and a 2.0 M LDA solution in THF (1.12 mL, 2.2 mmol) was added dropwise over ∼5 min; the resulting mixture was stirred at −78 °C for at least 2 h. After addition of aldehyde, the reaction was stirred at −78 °C for ∼15 min and then slowly (∼30 min) warmed to 0 °C and stirred at 0 °C for ∼1 h. The reaction was then quenched at 0 °C with saturated NH_4Cl solution (∼30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extracts were dried over Na_2SO_4 and concentrated in vacuo, affording 0.860 g of crude alcohol **25** as a greenish foam. The foam and 50 mL of a 3:1:1 mixture of AcOH/THF/H_2O were stirred together at ∼50 °C for ∼3 h. The reaction was then cooled on ice, made strongly basic with 20% NaOH solution (∼120 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo, affording 534 mg of brown oil. The crude oil (534 mg), ammonium acetate (1.84 g, 23.8 mmol, Aldrich, 99.99+%), 60 mL of anhydrous THF, and 6 mL of glacial acetic acid were refluxed together with stirring under air for ∼3 h. The reaction was then cooled on ice and made strongly basic with a 2 M NaOH solution, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layer and extracts were dried over Na_2SO_4 and concentrated in vacuo, affording a yellow oil. Flash column chromatography using a 5 × 15 cm basic alumina column and eluting starting with 80:20 CH_2Cl_2/EtOAc, then with a small amount of 99:1 CH_2Cl_2/MeOH, and then with 98:2 CH_2Cl_2/MeOH (until the product comes out) afforded compound **26** (317 mg, 41% from compound **24**) as a beige solid: mp ≥120 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 2.41−5.14 (m, 11 H), 7.02−7.06 (m, 2H), 7.39 (t, 2H, J = 8.8 Hz), 8.52−8.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 26.6, 28.3, 30.9, 32.2, 43.4−45.7 (m), 53.5, 80.4, 123.0, 123.2, 130.1, 130.3, 131.8, 132.5, 135.1, 135.2, 138.8, 148.2, 148.4, 149.0, 149.4, 151.1, 151.2, 154.0; IR ($CDCl_3$) ν 3314 (br), 2976, 1688, 1412 cm^{-1}. HRMS (FAB) calcd for $C_{26}H_{27}N_4O_2$ (MH^+) 427.2134, found 427.2134.

6,7,8,9,9a,10-Hexahydro-5*H*-pyrido[3,4,5-*de*]quino[8,7-*b*][1,10]phenanthroline Trihydrochloride (1). Compound **26** (258 mg, 0.600 mmol) and 30 mL of a 1:3 mixture of HCl (concentrated) and EtOAc were stirred together at room temperature for ∼3 h. Solvents were then removed in vacuo with heating, and 3 mL of MeOH was added. The resulting yellow suspension was cooled on dry ice and vacuum filtered. The flask and precipitate were washed with 6 mL of dry-ice-cold MeOH. The precipitate was dried under air, affording the tri-HCl salt of compound **1** (132 mg, 50%) as a beige solid: mp ≥280 °C dec; ^{1}H NMR (500 MHz, D_2O) δ 3.13−3.54 (m, 7H), 3.88−3.95 (m, 1H), 4.07 (dd, 1H, J = 12.0, 5.0 Hz), 4.64 (d, 1H, J = 17.0 Hz), 4.76 (d, 1H, J = 17.0 Hz), 8.05 (dd, 1H, J = 8.0, 6.0 Hz), 8.09 (dd, 1H, J = 8.0, 6.0 Hz), 8.58 (d, 1H, J = 8.0 Hz), 8.62 (d, 1H, J = 8.0 Hz), 8.81 (d, 1H, J = 6.0 Hz), 8.87 (d, 1H, J = 6.0 Hz); ^{13}C NMR (125 MHz, D_2O) δ 22.6, 25.2, 29.2, 30.0, 43.1, 44.7, 128.5, 128.7, 133.1, 137.0, 137.4, 138.7, 139.4, 140.8, 141.4, 142.4, 143.5, 144.3, 147.8, 147.9 (signals for two carbon atoms appear to be coincident); IR (KBr) ν 3423 (br), 3034−2404, 1612, 1569, 1534, 1426, 1303 cm^{-1}. HRMS (FAB) calcd for $C_{21}H_{19}N_4$ (MH^+) 327.1610, found 327.1610. Anal. Calcd for $C_{21}H_{21}Cl_3N_4$: C, 57.88; H, 4.86; Cl, 24.41; N, 12.86. Found: C, 57.53; H, 4.72; Cl, 24.73; N, 12.64.

4-Prop-2-enoylbenzenecarbonitrile (28). CAUTION: Because of the toxicity of tin species, this reaction must be done in the hood with the exhaust fan operating at maximum speed.

4-Cyanobenzoyl chloride **27** (9.00 g, 54.3 mmol, Aldrich), *trans*-benzyl(chloro)bis(triphenylphosphine)palladium(II) (412 mg, 1 mol %, Aldrich), 100 mL of anhydrous $CHCl_3$ (stabilized by amylenes), and tributyl(vinyl)tin (15.9 mL, 54.3 mmol, Aldrich) were placed, in the above order, into a 250 mL round-bottomed flask and refluxed under air for ∼2 h. The reaction was then cooled and 100 mL of half-saturated aqueous KF solution was added. The resulting jelly-like mixture was vigorously magnetically stirred for ∼15 min and vacuum filtered through Celite into a 500 mL or a 1 L filter flask (note: foaming). The Celite was washed with $CHCl_3$. The combined filtrate and wash were separated to give an organic layer and an aqueous layer. The aqueous layer was extracted with $CHCl_3$ once. A fresh 100 mL of half-saturated KF solution was added to the combined organic layer and extract. The resulting mixture was vigorously magnetically stirred for ∼15 min and vacuum filtered through Celite into a 500 mL or a 1 L filter flask (note: foaming). The Celite was washed with $CHCl_3$. The combined filtrate and wash were separated to give an organic layer and an aqueous layer. The aqueous layer was extracted with $CHCl_3$ once. The combined organic layer and extract were adsorbed on silica (∼30 g), solvent was removed in vacuo, and the resulting yellow powder was loaded onto a 6 × 26 cm silica column. Elution with 90:10 hexane/EtOAc (∼1 L) and then with 80:20 hexane/EtOAc (∼2 L) afforded compound **28** (4.40 g, 60%) as a light yellow solid, which is unstable and sensitive to heat, forming a polymer-like insoluble white material. The light yellow solid, which contains a small amount of Bu_3SnCl, was immediately used for the next reaction without further purification. An analytical sample was prepared using preparative silica TLC (1000 μm 20 × 20 cm plate, 80:20 EtOAc/hexanes) as a white solid: mp 53−54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (dd, 1H, J = 10.8, 1.2 Hz), 6.44 (dd, 1H, J = 17.0, 1.2 Hz), 7.09 (dd, 1H, J = 17.0, 10.8 Hz), 7.77 (d, 2H, J = 8.4 Hz), 7.99 (d, 2H, J = 8.4 Hz); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 116.2, 118.0, 129.0, 131.7, 132.0, 132.5, 140.4, 189.6; IR ($CDCl_3$) ν 2230, 1672 cm^{-1}. Anal. Calcd for $C_{10}H_7NO$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.36; H, 4.61; N, 8.85.

4-[3-(2-Oxocyclohexyl)propanoyl]benzenecarbonitrile (29). α,β-Unsaturated ketone **28** (4.38 g, 27.9 mmol), 50 mL of anhydrous CH_2Cl_2, and 1-cyclohexenyloxytrimethylsilane (6.78 mL, 34.8 mmol, Aldrich) were placed together under argon into a 100 mL round-bottomed flask in the above order. The resulting solution was then added through a cannula to a stirred suspension of $SnCl_2$ (6.86 g, 36.2 mmol) in 10 mL of anhydrous CH_2Cl_2 cooled to −78 °C (after the addition, the flask that contained **28** was washed with 20 mL of anhydrous CH_2Cl_2 and the wash was added to the reaction flask; small amounts of insoluble "polymeric" starting material are usually left in the original flask). Trimethylsilyl chloride (8.55 mL, 66.9 mmol) was then added all at once and the reaction was stirred at −78 °C for ∼30 min and then at room temperature for ∼1.5 h. The reaction was then quenched with 10% citric acid (∼30 mL), the layers were separated, and the aqueous layer was extracted with EtOAc twice. The organic layer and extracts might have small amounts of insoluble "polymeric" starting material, which is filtered off after drying over Na_2SO_4. The combined organic layer and extracts were adsorbed on silica (∼25 g) and, after removal of volatiles, loaded onto a 6 × 20 cm silica column. Elution with 75:25 hexanes/EtOAc afforded diketone **29** (5.30 g, 75%) as a light yellow oil, which was immediately used for the next reaction. An analytical sample was prepared using preparative TLC (1000 μm 20 × 20 cm plate, 80:20 EtOAc/hexanes) as a white solid: mp 58−59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35−1.45 (m, 1H), 1.58−1.70 (m, 3H), 1.82−1.84 (m, 1H), 1.97−2.11 (m, 3H), 2.23−2.42 (m, 3H), 2.87−2.95 (m, 1H), 3.07−3.14 (m, 1H), 7.71 (d, 2H, J = 8.4 Hz), 8.02 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 25.3, 28.2, 34.8, 36.9, 42.4, 49.9, 116.1, 117.9, 128.5, 132.4, 139.6, 198.6, 212.8; IR ($CDCl_3$) ν 2229, 1699 cm^{-1}. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.05; H, 6.64; N, 5.40.

4-[2-(5,6,7,8-Tetrahydroquinolyl)]benzenecarbonitrile (30). Diketone **29** (3.94 g, 15.4 mmol), ammonium acetate (3.57 g, 46.3 mmol, Aldrich, 99.99+%), and 50 mL of glacial acetic acid were placed together into a 100 mL round-bottomed flask. The reaction was refluxed with stirring under argon overnight. The reaction was then cooled on ice, made strongly basic with a 20% NaOH solution, and extracted with EtOAc (3 × 100 mL). The combined extracts were dried over Na_2SO_4 and adsorbed on silica (∼15 g). Purification by flash column chromatography using a 5 × 20 cm silica column and eluting with 90:10 hexanes/EtOAc afforded compound **30** (1.52 g, 42%) as a white solid: mp 96−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77−1.83 (m, 2H), 1.87−1.93 (m, 2H), 2.77 (t, 2H, J = 6.4 Hz), 2.95 (t, 2H, J = 6.4 Hz), 7.41 (d, 1H, J = 8.0 Hz), 7.43 (d, 1H, J = 8.0 Hz), 7.65 (d, 2H, J = 8.4 Hz), 8.03 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 23.2, 28.7, 32.9, 111.6, 118.1, 118.9, 127.1, 132.2, 137.5, 143.7, 151.8, 157.6; IR ($CDCl_3$) ν 2227, 1460 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.72; H, 6.01; N, 11.79.

4-[2-(8-Oxo-5,6,7-trihydroquinolyl)]benzenecarbonitrile (31). Compound **30** (1.75 g, 7.45 mmol), benzaldehyde (2.27 mL, 22.4 mmol), and acetic anhydride (2.82 mL, 29.8 mmol) were placed together into a 25 mL round-bottomed flask fitted with a condenser, and the reaction was refluxed with stirring under argon overnight (temperature of oil bath is ∼160 °C). The reaction was then diluted with 30 mL of CH_2Cl_2 and 30 mL of water and made strongly basic with 2 M NaOH, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layer and extracts were dried over Na_2SO_4 and concentrated in vacuo, affording crude olefin (4.00 g) as a yellow oil, which contains some benzaldehyde. The crude oil was then dissolved in 15 mL of anhydrous CH_2Cl_2 and 30 mL of anhydrous MeOH. Ozone generated using the Osmonics system set at 1 amp with an oxygen flow rate of 2 L/min was bubbled through at ca. −40 °C with stirring for ∼20 min (until disappearance of the starting material as judged by TLC on silica eluting with 80:20 hexanes/EtOAc). The reaction was then purged with argon for ∼10 min and quenched with 10 mL of anhydrous dimethyl sulfide. The reaction was then allowed to warm slowly to room temperature and left to stir overnight under argon. Most of the solvent was then removed on a rotary evaporator and the insoluble white powder was collected, affording 0.930 g of quinolone **31**. The filtrate was concentrated in vacuo, affording 3.58 g of yellow oil, to which 10 mL of 80:20 hexanes/EtOAc and 2−3 mL of MeOH were added. A second crop was collected, affording 0.170 g of quinolone **31** as a white powder. The combined product (1.10 g, 60%) was used for the next reaction without further purification: mp 192−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (p, 2H, J = 6.4 Hz), 2.81 (t, 2H, J = 6.4 Hz), 3.06 (t, 2H, J = 6.4 Hz), 7.70 (d, 2H, J = 8.8 Hz), 7.76 (d, 1H, J = 8.0 Hz), 7.83 (d, 1H, J = 8.0 Hz), 8.14 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 29.2, 40.1, 112.6, 118.7, 124.1, 127.7, 132.5, 138.9, 140.4, 142.5, 148.1, 154.2, 196.2; IR ($CDCl_3$) ν 2229, 1705 cm^{-1}. Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.72; H, 4.87; N, 11.27.

4-[2-(5,6-Dihydro-8-oxo-7-{[4-(phenylmethoxy)phenyl]-methylene}quinolyl)]benzenecarbonitrile (32). Quinolone **31** (1.10 g, 4.43 mmol), 4-benzyloxybenzaldehyde (1.22 g, 5.76 mmol, Aldrich, 97%), and 85% KOH pellets (1.14 g, 20 mmol) were placed together into a 100 mL round-bottomed flask; 70 mL of anhydrous MeOH was added and then the reaction was heated at reflux with stirring under argon for ∼3 h. The reaction was then cooled on ice and the solid was collected by vacuum filtration and washed with anhydrous MeOH (3 × 5 mL), affording compound **32** (1.63 g, 83%) as a bright yellow solid. The compound is somewhat unstable and was immediately used for the next reaction without further purification: mp 228−230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (t, 2H, J = 6.0 Hz), 3.20 (t, 2H, J = 6.0 Hz), 5.11 (s, 2H), 7.03 (d, 2H, J = 8.8 Hz), 7.32−7.46 (m, 7H), 7.75 (d, 2H, J = 8.4 Hz), 7.76 (d, 1H, J = 7.8 Hz), 7.85 (d, 1H, J = 7.8 Hz), 7.95 (s, 1H), 8,21 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 27.8, 70.2, 112.8, 115.1, 119.0, 123.9, 127.6, 127.9, 128.3, 128.4, 128.9, 132.2, 132.7, 133.3, 136.6, 138.3, 138.7, 138.9, 142.9, 149.7, 154.9, 159.7, 186.3; IR ($CDCl_3$) ν 2229, 1666, 1578, 1511, 1173 cm^{-1}. HRMS (FAB) calcd for $C_{30}H_{23}N_2O_2$ (MH^+) 443.1760, found 443.1758.

4-{7-[4-(Phenylmethoxy)phenyl]-5,6,8,9-tetrahydropyridino[3,2-*h*]quinolino[8,7-*b*]quinolin-2-yl}benzenecarbonitrile (33). Compound **32** (793 mg, 1.77 mmol) and quinolone **4**[10] (264 mg, 1.77 mmol) were placed together in a 25 mL round-bottomed flask under argon. BF_3•Et_2O (8 mL) was added and the resulting blood-red solution was vigorously stirred overnight. The reaction was then diluted with 50 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ solution twice (**CAUTION**: violent gas evolution!), dried over Na_2SO_4, and concentrated in vacuo, affording the intermediate diketone (1.09 g, 1.85 mmol) as a yellow foam. The diketone was placed into a 100 mL round-bottomed flask, ammonium acetate (427 mg, 5.55 mmol, Aldrich, 99.99+%) and 30 mL of glacial acetic acid were added, and the reaction was refluxed with stirring under argon for ∼8 h or overnight. The reaction was then cooled on ice, made strongly basic with a 20% NaOH solution, and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo, affording 1.08 g of crude **2** as a purple solid. Flash column chromatography using a 5 × 20 cm basic alumina column and eluting starting with 80:20 CH_2Cl_2/EtOAc (until all dark purple impurities elute), then with a small amount of 99:1 CH_2Cl_2/MeOH, and then with 98:2 CH_2Cl_2/MeOH (until the product elutes) afforded compound **33** (554 mg, 54%) as a pink-beige foam: mp 210 °C slow dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.71−2.86 (m, 4H), 2.88−2.95 (m, 4H), 5.14 (s, 2H), 7.11−7.15 (m, 4H), 7.22−7.26 (m, 1H), 7.35−7−38 (m, 1H), 7.43 (t, 2H, J = 7.5 Hz), 7.49 (d, 2H, J = 7.5 Hz), 7.54 (d, 1H, J = 7.5 Hz), 7.66 (s, 2H), 7.77 (d, 2H, J = 8.5 Hz), 8.26 (d, 2H, J = 8.5 Hz), 8.72 (d, 1H, J = 4.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6, 27.6, 70.3, 112.2, 115.2, 119.3, 121.5, 123.8, 127.7, 128.3, 128.4, 128.9, 129.5, 130.0, 132.5, 132.6, 133.4, 133.5, 133.7, 133.8,

135.8, 136.8, 143.7, 147.9, 148.7, 150.3, 150.6, 152.3, 152.9, 155.1, 158.7; IR ($CDCl_3$) ν 3355 (br), 2229, 1609, 1512, 1242 cm^{-1}. HRMS (FAB) calcd for $C_{39}H_{29}N_4O$ (MH^+) 569.2341, found 569.2341.

4-{7-(4-Hydroxyphenyl)-5,6,8,9-tetrahydropyridino-[3,2-*h*]quinolino[8,7-*b*]quinolin-2-yl}benzoic Acid (34). Compound **33** (412 mg, 0.720 mmol) and 4 M HCl (24 mL) were placed into a 50 mL round-bottomed flask. The resulting sticky suspension was refluxed overnight with stirring, then it was cooled on ice, and the solid was collected by vacuum filtration. The precipitate was washed with 10 mL of cold water and 10 mL of CH_2Cl_2, affording compound **34** (314 mg, 81%) as a ~1:1 mixture of mono- and di-HCl salts (determined by combustion analysis) mp 210 °C slow dec; ^{1}H NMR (500 MHz, CD_3OD) δ 3.01−3.06 (m, 4H), 3.19−3.27 (m, 4H), 7.02 (d, 2H, J = 8.5 Hz), 7.19 (d, 2H, J = 8.5 Hz), 7.98 (dd, 1H, J = 8.0, 6.0 Hz), 8.14 (d, 1H, J = 8.0 Hz), 8.18 (d, 2H, J = 8.5 Hz), 8.25 (d, 2H, J = 8.5 Hz), 8.33 (d, 1H, J = 8.0 Hz), 8.47 (d, 1H, J = 8.0 Hz), 8.84 (d, 1H, J = 6.0 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 25.5, 25.9, 26.5, 26.8, 117.2, 126.7, 127.0, 128.3, 130.0, 130.4, 131.0, 131.4, 131.6, 134.1, 137.5, 138.3, 139.1, 139.2, 142.5, 143.8, 144.1, 146.1, 146.3, 148.1, 153.8, 155.2, 159.8, 168.9; IR (KBr) ν 3388 (br), 1705, 1611, 1271, 1230 cm^{-1}. HRMS (FAB) calcd for $C_{32}H_{24}N_3O_3$ (MH^+) 498.1818, found 498.1816. Anal. Calcd for $C_{32}H_{24}ClN_3O_3$: C, 71.97; H, 4.53; Cl, 6.64; N, 7.87. Anal. Calcd for $C_{32}H_{25}Cl_2N_3O_3$: C, 67.37; H, 4.42; Cl, 12.43; N, 7.37. Found: C, 70.53; H, 4.47; Cl, 9.01; N, 7.95.

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Supporting Information Available: Experimental details for the preparation of compounds **4**, **5**, **6**, **6a**, **7**, **8**, **8a**, **9**, and **10** and ^{1}H and ^{13}C NMR spectra of compounds **6**, **6a**, **8**, **8a**, **10**, **23-26**, **1**, and **32**−**34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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