JOC Article

A Photochemical Approach to the Galanthan Ring System

David E. Minter* and Christopher D. Winslow

Department of Chemistry, Texas Christian University, Fort Worth, Texas 76129

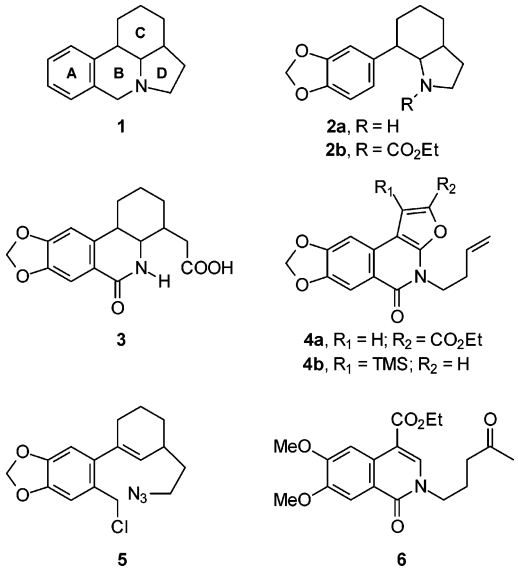
d.minter@tcu.edu

Received November 10, 2003

A five-step, atom-efficient synthesis of the Galanthan tetracyclic skeleton has been developed. The key step is an unusual intramolecular de Mayo reaction using an isocarbostyril substrate with a functionalized tether on nitrogen. The target molecule is produced in 35% overall yield from isocarbostyril.

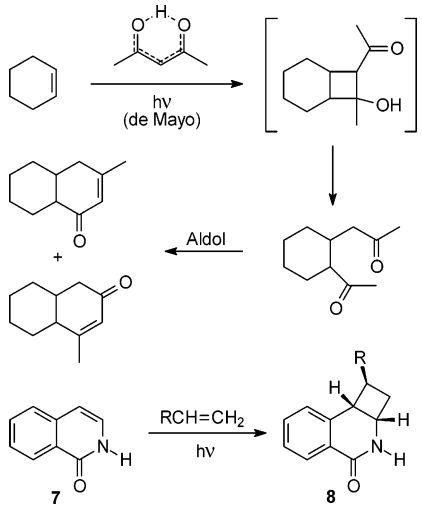
Introduction

The galanthan skeleton (**1**) is the central core for the lycorine-type *Amaryllidaceae* alkaloids.[1] Among the numerous strategies used for constructing this unit, closure of the B-ring at a late stage in the synthesis with substrates such as **2** is a historically important method.[2] Late-stage formation of the D-ring using phenanthridinone derivatives (i.e., **3**) has also been shown.[3] The simultaneous formation of two rings, C and D for example, is demonstrated effectively by the intramolecular Diels–Alder reaction[4] of **4**, and multiple ring closures employing tandem reactions with precursors such as **5** and **6** have been reported.[5] There are several approaches to B-ring construction using radical[6] and photochemical[7] cyclizations.



The strategy of using carbon atoms contained in a tether on nitrogen of an isocarbostyril (i.e., **6**) to provide requisite ring components is especially intriguing. Since photoannelations[8] using the de Mayo reaction[9] have already been shown to produce cyclohexenones from alkenes and β-dicarbonyl compounds, a modification of **6** that integrates a 1,3-dione into the tether may provide an unusual entry to the galanthan skeleton via a parallel approach. To that end, the suitability of isocarbostyrils as substrates for the de Mayo reaction has been evaluated using both an intermolecular model as well as a tethered dione system to test the intramolecular version.

SCHEME 1



Results and Discussion

The classic de Mayo reaction involves the [2 + 2] photocycloaddition of an alkene to the hydrogen-bonded enol tautomer of a β-dicarbonyl compound. The resulting cyclobutanol opens spontaneously to a δ-dicarbonyl product that cyclizes under aldol conditions to cyclohexenones (Scheme 1). Although this procedure has not been reported using an isocarbostyril as a substrate, cyclobutanes derived from [2 + 2] photocycloadditions of **7** and

* Corresponding author.

(1) For excellent reviews of lycorine-type alkaloid syntheses, see: (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, pp 251–376. (b) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, pp 323–423.

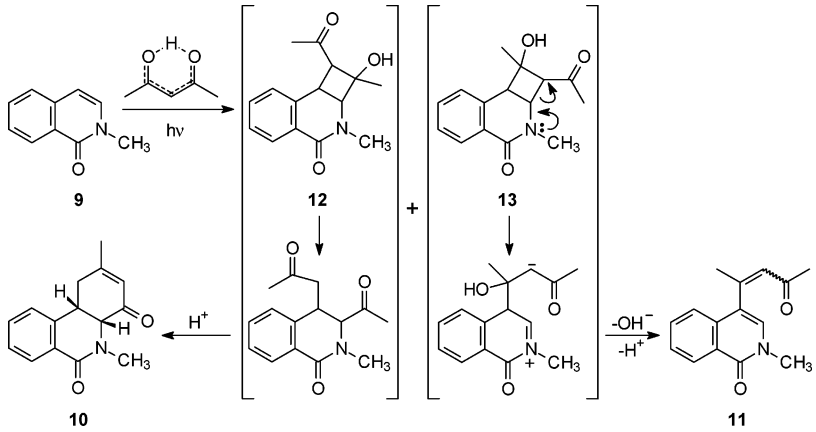
(2) (a) Hill, R. K.; Joule, J. A.; Loeffler, L. J. *J. Am. Chem. Soc.* **1962**, *84*, 4951–4956. (b) Martin, S. F.; Tu, C.-y. *J. Org. Chem.* **1981**, *46*, 3764–3767. (c) Banwell, M. G.; Harvey, J. E.; Hockless, D. C. R. *J. Org. Chem.* **2000**, *65*, 4241–4250.

(3) Irie, H.; Nishitani, Y.; Sugita, M.; Tamoto, K.; Uyeo, S. *J. Chem. Soc., Perkin Trans. 1* **1972**, 588–590.

(4) (a) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595–3607. (b) Boger, D. L.; Wolkenberg, S. E. *J. Org. Chem.* **2000**, *65*, 9120–9124. (c) Wolkenberg, S. E.; Boger, D. L. *J. Org. Chem.* **2002**, *67*, 7361–7364.

10.1021/jo0356560 CCC: $27.50
Published on Web 02/06/2004

SCHEME 2

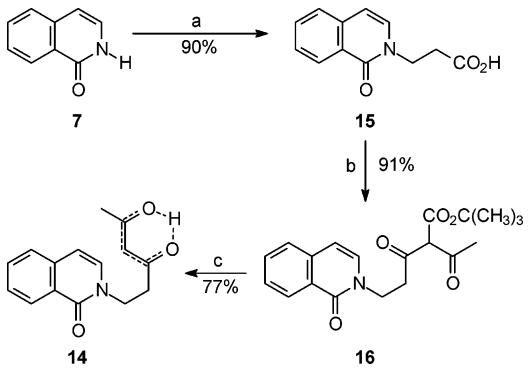


electron-deficient, polarized alkenes of the general formula CH_2═CHR for R = CN, Cl, C(═O)CH_3, and CO_2-CH_3 are produced regio- and stereoselectively in favor of the so-called "head-to-tail" regioisomer **8** and the exo orientation of the group R.[10]

To evaluate an isocarbostyril as a de Mayo substrate, **9** was irradiated with a large excess of 2,4-pentanedione and the resulting mixture of ketones was treated with alcoholic HCl under aldol conditions (Scheme 2). Chromatographic separation gave two major products, **10** and **11**, isolated as pure crystalline solids in 38 and 46% yields, respectively, and two inseparable minor products constituting 14% of the total mass.[11]

The ketone **10** is one of two possible products of a photoannelation sequence arising from a "head-to-tail" approach of the enol to **9** and subsequent aldol condensation, thus making the acid-catalyzed aldol addition step surprisingly regioselective. A homonuclear spin decoupling experiment involving irradiation of the vinyl proton at 5.86 ppm δ of **10** results in the removal of allylic coupling with the geminal methylene protons at 3.06 and 2.93 ppm δ. This observation is consistent with **10** but not the alternative photoannelation isomer, where the methylene group is not allylic. The cis ring fusion in **10** is clearly established by the ^{1}H NMR coupling constant (J = 5.3 Hz) for the vicinal tertiary protons. Although **11** is a single isomer, the double-bond geometry is not determined definitively using NMR analysis.

SCHEME 3. Synthesis of 14[a]



[a] Reagents: (a) CH_2═$CHCO_2CH_3$, cat. $CH_3O^-Na^+$; then 1 N HCl, reflux. (b) $SOCl_2$; then $CH_3COCH_2CO_2C(CH_3)_3$, NaH. (c) TsOH, benzene, reflux.

Ketone **11**, which is not an annelation product, probably results from a reversal of the regiochemistry in the photocycloaddition step.[12] Although there is no direct evidence for **13**, the ring-opening elimination pathway presented in Scheme 2 depicts a reasonable mechanism that not only explains the formation of **11** but is also unavailable to **12**. If valid, this process must operate faster than the normal retro aldol ring opening in the de Mayo sequence.

By incorporating a β-diketone into the six-carbon tether on nitrogen, the isocarbostyril **14** becomes a precursor to the basic galanthan skeleton provided that the photocyclization step favors one of four possible regiochemical modes. The synthesis of **14** begins with a Michael addition of isocarbostyril anion to methyl acrylate followed by hydrolysis of the resulting ester (Scheme 3). The acid chloride derived from **15** is used to acylate sodium *tert*-butyl acetoacetate in ether resulting in a >11:1 mixture of the desired ester **16** and the product of O-acylation. In THF solvent, the ratio is only 2:1 in favor of **16**. Cleavage of the ester with an accompanying decarboxylation completes the synthesis of **14** in 63% yield over four steps from **7**.

(5) (a) Wenkert, E.; Chawla, H. P. S.; Schell, F. M. *Synth. Commun.* **1973**, *3*, 381−386. (b) Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 6783−6789.

(6) (a) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 7904−7905. (b) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 6210−6219. (c) Jabin, I.; Netchitailo, P. *Tetrahedron Lett.* **2001**, *42*, 7823−7827. (d) Ishizaki, M.; Kai, Y.; Hoshino, O. *Heterocycles* **2002**, *57*, 2279−2297.

(7) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1979**, *44*, 1236−1241.

(8) (a) Baldwin, S. W.; Gawley, R. E.; *Tetrahedron Lett.* **1975**, *16*, 3969−3972. (b) Baldwin, S. W.; Gawley, R. E.; Doll, R. J.; Leung, K. H. *J. Org. Chem.* **1975**, *40*, 1865−1867.

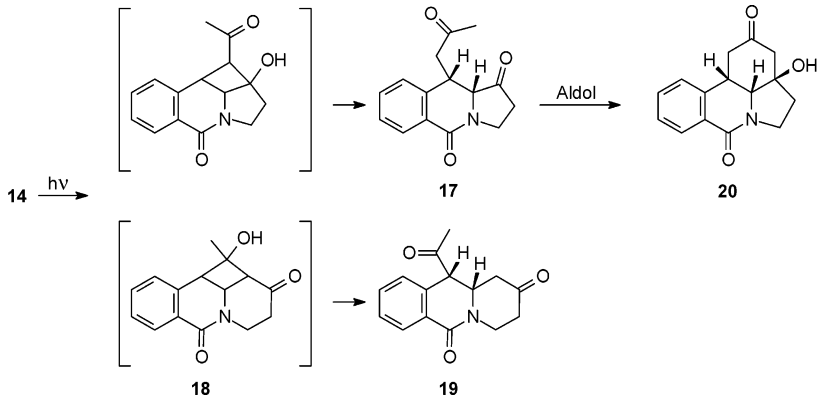
(9) (a) de Mayo, P.; Takeshita, H. *Can. J. Chem.* **1963**, *41*, 440−449. (b) de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41−47.

(10) (a) Chiba, T.; Takada, Y.; Kaneko, C.; Kiuchi, F.; Tsuda, Y. *Chem. Pharm. Bull.* **1990**, *38*, 3317−3325. (b) Kurita, J.; Yamanaka, T.; Tsuchiya, T. *Heterocycles* **1991**, *32*, 2089−2092. (c) Al-Jalal, N.; Dres, M. G. B.; Gilbert, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 965−966. (d) Al-Jalal, N.; Covell, C.; Gilbert, A. *J. Chem. Res., Synop.* **1998**, 678. (e) Al-Jalal, N.; Covell, C.; Gilbert, A. *J. Chem. Res., Miniprint* **1998**, 2912−2924.

(11) One of the two minor products is clearly the geometric isomer of **11**. Heating a mixture of the two minor products in dilute HCl causes the appearance of **11** at the expense of this component as determined by following the reaction with TLC and NMR analysis. The other minor product has the NMR characteristics of the isomer of **10** with a trans ring fusion.

(12) The loss of regioselectivity with 2,4-pentanedione is not unexpected since the hydrogen-bonded enol tautomer with its symmetrically delocalized π-system represents essentially a nonpolarized alkene.

SCHEME 4



Of the four regiochemical modes by which the unsymmetrical enol π-system can approach the isocarbostyril double bond, only two are likely due to the strong preference for parallel addition as opposed to cross addition in these reactions.[13,14] One of these modes leads to the galanthan ring system precursor **17** and the other to the isomeric dione **19** (Scheme 4). The ring-opening pathway postulated for **13** is not likely to supplant the normal retro aldol process in **18** since the result would be a highly strained anti-Bredt structure. Kinetics of intramolecular photocyclizations favor five-membered rings[14] leading to the expectation that **17** will be the observed product. Although the examination of molecular models reveals no geometrical constraints on the formation of either product, **17** appears to be more favorable in this analysis as well.

Irradiation of **14** in acetonitrile for 1.5 h gives a single product **17** in greater than 70% yield after purification by flash chromatography. The cis stereochemistry of the vicinal tertiary ring protons in **17** is clearly evident from the vicinal coupling constant (J = 4.4 Hz) in the proton NMR spectrum. Dione **17** is differentiated from **19** by the presence of the acetonyl group consisting of a methyl carbon (30.8 ppm δ), a carbonyl carbon (205.2 ppm δ), and a methylene carbon (44.1 ppm δ) with the appropriate 2- and 3-bond C−H correlations in the HMBC spectrum.

Ring closure to the galanthan derivative **20** is carried out under basic conditions with piperidine in benzene at reflux in 78% yield after purification by flash chromatography. This ketone is produced as a single diastereomer, the structure of which is dictated by the fact that only the endo face of the carbonyl carbon at C-1 in **17** is accessible to attack during the aldol addition. Thus, the hydroxyl group in **20** is β as shown.

This five-step, atom-efficient synthesis of the galanthan skeleton from **7** is accomplished in 35% overall yield and incorporates a unique application of the intramolecular de Mayo reaction with an isocarbostyril substrate. With the synthesis of **17**, this route to the galanthan ring system intersects Bruce Ganem's previously published approach to the lycorine skeleton[15] and provides an attractive alternative to constructing the tetracyclic core found in this series of alkaloids.

Experimental Section

Commercially available reagents were used without further purification unless otherwise noted. THF was doubly distilled, first from calcium hydride and subsequently from sodium benzophenone ketyl under nitrogen. Acetonitrile was distilled from calcium hydride and stored over 4 Å molecular sieves under nitrogen. Column chromatography was performed using ICN Woelm Pharma silica gel (32−63 μm), and thin-layer chromatography was done using silica gel (250 μm) on polyester TLC plates. Melting points were determined on a Thomas−Hoover capillary melting point apparatus and are uncorrected. Mass spectra were recorded with an ionization energy of 70 eV using GC injection with helium as the carrier gas. All NMR spectra were acquired from 0.2 M solutions in $CDCl_3$ at 25 °C with a 400 MHz spectrometer operating at 399.968 MHz for ^{1}H and 100.581 MHz for ^{13}C and referenced to 0.1% internal TMS.

Photochemical reactions were carried out in Pyrex tubes attached to a water-cooled Pyrex immersion well containing a 500W medium-pressure Hanovia mercury arc lamp.

Irradiation of 9 and 2,4-Pentanedione. *N*-Methylisocarbostyril (**9**) was prepared from isoquinoline in 73% yield using a modification of the published procedure.[16] A solution containing **9** (600 mg, 3.77 mmol), 2,4-pentanedione (14.6 g, 146 mmol), and benzene (180 mL) was purged with nitrogen for 20 min and cooled to 15 °C before irradiation through a Pyrex filter for 48 h. The reaction mixture was concentrated by rotary evaporation and then placed on a mechanical pump for 21 h. The viscous amber oil was dissolved in a solution containing 7 mL of concentrated HCl in 100 mL of 95% ethanol and heated at reflux with stirring for 2 h. The resulting black solution was concentrated under reduced pressure, and the crude product was redissolved in 50 mL of dichloromethane. This solution was then washed successively with saturated sodium bicarbonate (2 × 40 mL) and saturated sodium chloride (40 mL), dried over sodium sulfate, filtered, and concentrated. TLC analysis of the residue (silica, ethyl acetate−diethyl ether, 1:1) identified four products with R_f values of 0.22, 0.34, 0.35, and 0.45. The middle spots proved to be inseparable by column chromatography (silica, ethyl acetate−diethyl ether, 1:1), while **10** (R_f = 0.22, 344 mg, 38%) and **11** (R_f = 0.45, 420 mg, 46%) were obtained as off-white crystalline solids.

2,5-Dimethyl-1,4a,5,10b-tetrahydrophenanthridine-4,6-dione (10): R_f = 0.22; mp 161−163 °C; IR (KBr) 1674, 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05 (3H, dd, J = 1.3, 0.9 Hz), 2.93 (1H, dddq, J = 18.9, 4.8, 2.3, 0.9 Hz), 3.06 (1H, br dd, J =

(13) (a) Becker, D.; Harel, Z.; Nagler, M.; Gillon, A. *J. Org. Chem.* **1982**, *47*, 3297−3306. (b) Dauben, W. G.; Shapiro, G. *Tetrahedron Lett.* **1985**, *26*, 989−992.

(14) (a) Srinivasan, R.; Carlough, K. H. *J. Am. Chem. Soc.* **1967**, *89*, 4932−4936. (b) Liu, R. S. H.; Hammond, G. S. *J. Am. Chem. Soc.* **1967**, *89*, 4936−4944.

(15) Ganem, B. *Tetrahedron Lett.* **1971**, *12*, 4105−4108.

(16) Spassov, S. L.; Atanassova, I. A.; Haimova, M. A. *Org. Magn. Reson.* **1984**, *22*, 194−197.

18.9, 3.3 Hz), 3.30 (3H, s, NCH_3), 3.92 (1H, dddd, J = 5.3, 4.8, 3.3, 0.5 Hz), 4.09 (1H, d, J = 5.3 Hz), 5.86 (1H, dq, J = 2.3, 1.3 Hz), 7.14 (1H, bd, J = 7.6 Hz), 7.34 (1H, ddd, J = 7.7, 7.5, 1.2 Hz), 7.43 (1H, ddd, J = 7.6, 7.5, 1.6 Hz), 8.09 (1H, ddd, J = 7.7, 1.5, 0.5 Hz); ^{13}C NMR δ 24.6 (q), 32.6 (t), 35.8 (q), 37.8 (d), 65.7 (d), 123.0 (d), 127.1 (d), 127.7 (d), 129.1 (d), 130.0 (s), 131.9 (d), 136.7 (s), 159.5 (s), 164.1(s), 194.8 (s). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27. Found: C, 74.41; H, 6.10.

2-Methyl-4-(4-oxo-2-penten-2-yl)isoquinolin-1(*2H*)-one (11): R_f = 0. 45; mp 115−118 °C; IR (KBr) 1674, 1651, 1624, 1593, 1352, 1192, 772, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.30 (3H, s), 2.50 (3H, d, J = 1.3 Hz), 3.63 (3H, s, NCH_3), 6.38 (1H, q, J = 1.3 Hz), 7.02 (1H, s), 7.50−7.55 (2H, complex), 7.67 (1H, ddd, J = 8.1, 7.0, 1.5 Hz), 8.49 (1H, dd, J = 8.1, 1.5 Hz); ^{13}C NMR δ 21.6 (q), 32.1 (q), 37.0 (q), 121.7 (s), 124.3 (d), 127.2 (d), 126.0 (s), 127.6 (d), 128.3 (d), 130.2 (d), 132.2 (d), 134.9 (s), 151.1 (s), 162.1 (s), 198.6 (s). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27. Found: C, 74.30; H, 6.00.

2-(2-Carboxy-1-ethyl)isoquinolin-1(2*H*)-one (15). To a solution containing **7** (11.3 g, 78 mmol) and methyl acrylate (8.34 g, 97 mmol) in 150 mL of freshly distilled methanol was added sodium methoxide (419 mg, 7.8 mmol). The solution was warmed to a gentle reflux and stirred for 2.5 h. A second portion of methyl acrylate (8.34 g, 97 mmol) was added, and the solution was stirred at reflux for an additional 1.5 h. Concentrating the solution under reduced pressure gave a brown viscous oil, which was redissolved in dichloromethane (300 mL). This solution was washed successively with water (100 mL) and brine (2 × 100 mL), dried over sodium sulfate, filtered, and concentrated by rotary evaporation yielding a brown crystalline solid (16.3 g, 90.5%). A slurry of the crude ester (16.0 g, 69.2 mmol) in 150 mL of 1 N HCl was stirred at reflux for 1 h and an additional 16 h at ambient temperature. The solid product was removed by filtration, washed with water (2 × 30 mL), and dried while open to the atmosphere, giving a white crystalline solid (14.9 g, 99.2%), mp 127−129 °C. This material was suitable for use in the next step without further purification, although it could be recrystallized from benzene: IR (KBr) 2870, 1725, 1642, 1576, 1549, 795, 696 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.72 (2H, t, J = 7.0 Hz), 4.16 (2H, t, J = 7.0 Hz), 6.62 (1H, bd, J = 7.4 Hz), 7.48 (1H, d, J = 7.4 Hz), 7.51 (1H, ddd, J = 8.1, 7.0, 1.3 Hz), 7.65 (1H, bd, J = ~8.0 Hz), 7.71 (1H, ddd, J = 8.0, 7.0, 1.3 Hz), 8.23 (1H, dddd, J = 8.1, 1.3, 0.6, 0.6 Hz), 12.41 (1H, bs, OH); ^{13}C NMR (DMSO-d_6) δ 33.0 (t), 44.9 (t), 104.7 (d), 125.2 (s), 126.0 (d), 126.5 (d), 126.8 (d), 132.2 (d), 133.3 (d), 136.9 (s), 160.8 (s), 172.3 (s). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10. Found: C, 66.34; H, 5.22.

2-(4-Carbo-*tert*-butoxy-3,5-dioxo-1-hexyl)isoquinolin-1(2*H*)-one (16). A solution containing **15** (2.84 g, 13.1 mmol) and thionyl chloride (5.45 g, 45.8 mmol) in 60 mL of benzene was stirred at ambient temperature for 48 h. The resulting solution was concentrated under reduced pressure, redissolved in 100 mL of dry ethyl ether, and cooled in an ice−water bath. In a separate flask, *tert*-butyl acetoacetate (6.21 g, 39.2 mmol) was added to a slurry of oil-free sodium hydride (1.30 g, 54.2 mmol) in 80 mL of dry ethyl ether at 0° C. After stirring for 10 min at that temperature, a clear solution of the sodium salt of *tert*-butyl acetoacetate was obtained. The acid chloride solution was then transferred via a cannula, using nitrogen pressure, over a 10 min period into the second flask to produce a light brown mixture. The solution was warmed to ambient temperature, stirred for 1 h, and then poured into 100 mL of 1 N HCl cooled with an ice/water bath. The mixture was stirred for 15 min with cooling followed by the removal of the organic solvent by rotary evaporation. The resulting aqueous slurry was extracted with dichloromethane (2 × 50 mL). These organic extracts were combined, washed successively with sodium bicarbonate (1 × 50 mL) and brine (1 × 50 mL), dried over sodium sulfate, gravity filtered, and concentrated under reduced pressure. Flash chromatography (silica, ethyl acetate−hexane, 1:3) gave **16** (4.27 g, 91.4%) as a white solid, mp 89−91 °C, containing a trace of **15**, as well as the O-acylation product 3-[3-(1-oxo-1*H*-isoquinolin-2-yl)propionyloxy]but-2-enoic acid *tert*-butyl ester (291 mg, 6.23%) as a clear viscous oil. Dione **16** was used without further purification in the next step.

2-(3,5-Dioxo-1-hexyl)isoquinolin-1(2*H*)-one (14). A solution containing **16** (1.89 g, 5.3 mmol) and *p*-toluenesulfonic acid monohydrate (1.11 g, 5.8 mmol) in 100 mL of benzene was heated at reflux and stirred for 1.5 h. The solution was then cooled to ambient temperature, washed successively with saturated sodium bicarbonate (2 × 50 mL) and brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. Flash column chromatography (silica, ethyl acetate−hexane, 1:2) gave **14** as a white crystalline solid (1.04 g, 76.5%): mp 62−63 °C; IR (KBr) 1653, 1630, 1603, 785, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.99 (3H, s), 2.85 (2H, t, J = 6.5 Hz), 4.28 (2H, t, J = 6.5 Hz), 5.46 [1H, s, H-4′ (enol form)], 6.46 (1H, dd, J = 7.4, 0.7 Hz), 7.15 (1H, d, J = 7.4 Hz), 7.48 (1H, ddd, J = 8.0, 7.0, 1.3 Hz), 7.50 (1H, ddd, J = 8.0, 1.3, 0.7 Hz), 7.63 (1H, ddd, J = 8.0, 7.0, 1.4 Hz), 8.41 (1H, dddd, J = 8.0, 1.4, 0.7, 0.7 Hz), 15.36 [1H, bs, OH (enol form)]; ^{13}C NMR ($CDCl_3$) δ 24.4 (q), 37.4 (t), 45.9 (t), 100.9 (d), 105.9 (d), 125.9 (d), 126.1 (s), 126.8 (d), 127.6 (d), 132.2 (d), 132.4 (d), 137.1 (s), 162.2 (s), 190.1 (s), 191.8 (s). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88. Found: C, 69.85; H, 5.98.

10-(2-Oxopropyl)-2,3,10,10a-tetrahydropyrrolo[1,2-*b*]-isoquinolin-1,5-dione (17). A solution containing **14** (101 mg, 0.39 mmol) in 10 mL of acetonitrile was purged with nitrogen for 15 min prior to irradiation through a Pyrex filter at ambient temperature for 1.5 h. The reaction mixture was concentrated under reduced pressure by rotary evaporation. Flash chromatography (silica, ethyl acetate−hexane, 2:1) gave photoproduct **17** as a white crystalline solid (72.3 mg, 71.6%): mp 184−185 °C; IR (KBr) 1757, 1709, 1657, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.95 (3H, s), 2.47 (1H, dd, J = 16.3, 3.6 Hz), 2.63−2.73 (1H, complex), 2.68 (1H, dd, J = 16.3, 9.7 Hz), 2.77 (1H, dddd, J = 19.3, 8.9, 4.0, 0.8 Hz), 3.74 (1H, dddd, J = 12.5, 8.9, 8.9, 0.7 Hz), 3.91 (1H, ddd, J = 9.7, 4.4, 3.6 Hz), 4.23 (1H, bd of m, $J \approx$ 4.4 Hz), 4.39 (1H, dddd, J = 12.5, 10.0, 4.0, 0.7 Hz), 7.37−7.41 (2H, complex), 7.45 (1H, ddd, J = 8.0, 6.8, 1.5 Hz), 8.07 (1H, dd, J = 8.0, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 30.8 (q), 34.6 (d), 36.7 (t), 40.1 (t), 44.1 (t), 63.3 (d), 128.0 (d), 128.2 (d), 128.6 (d), 128.7 (s), 132.4 (d), 139.6 (s), 163.5 (s), 205.2 (s), 210.8 (s). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88. Found: C, 70.21; H, 5.97.

3a-Hydroxy-3,3a,4,5,11b,11c-hexahydro-1*H*-pyrrolo-[3,2,1-*de*]phenanthridine-2,7-dione (20). A solution containing **17** (104 mg, 0.4 mmol) and piperdine (172 mg, 2.0 mmol) in 15 mL of benzene was heated at reflux with stirring for 21 h. The solution was concentrated under reduced pressure by rotary evaporation. Flash column chromatography (silica, ethyl acetate−hexanes 10:1) gave an off-white crystalline product (80.8 mg, 77.7%): mp 235 °C (decomp.); IR (KBr) 3302, 1715, 1624 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.86−1.99 (2H, complex), 2.15 (1H, ddd, J = 14.1, 5.2, 1.8 Hz), 2.32 (1H, bd, J = 14.3 Hz), 2.42 (1H, dd, J = 14.1, 13.1 Hz) 2.77 (1H, d, J = 14.3 Hz), 3.54 (1H, ddd, J = 13.1, 5.2, 4.7 Hz), 3.62 (1H, ddd, J = 12.1, 9.2, 8.0 Hz), 3.73 (1H, ddd, J = 12.1, 9.0, 2.7 Hz), 3.83 (1H, bd, J = 4.7 Hz), 7.38−7.42 (2H, complex), 7.51 (1H, ddd, J = 8.1, 6.8, 1.5 Hz), 7.91 (1H, dd, J = 8.1, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 35.7 (d), 36.7 (t), 42.0 (t), 42.6 (t), 47.7 (t), 60.9 (d), 80.5 (s), 127.0 (d), 127.3 (d), 127.6 (d), 128.3 (s), 132.0 (d), 140.5 (s), 161.5 (s), 207.4 (s). Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88. Found: C, 69.64; H, 5.68.

Acknowledgment. This work was supported by The Welch Foundation (Grant P-1519 to D.E.M.).

JO0356560