Asymmetric Organic Synthesis. Radical Cyclizations of Chiral Enamides

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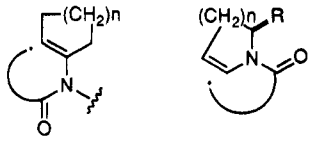
Stereoselective radical cyclizations to the enamide double bond have excellent potential for utilization in alkaloid and related nitrogen heterocycle synthesis. Complete facial selectivity has been found for radical cyclizations of chiral substrates **1a** → **2**, **7** → **8**, **11** → **12** + **13**, **15** → **16** + **17**, and **19** → **20**. The stereoselectivity for reduction of the intermediate tertiary radicals with Bu_3SnH correlates with product stability. For example, **7** gives cis-dihydro **8** with no trace of the trans-dihydro isomer **9**, 3.6 kcal/mol less stable than **8**. Radical cyclization of **11** gave a 1:1 mixture of the six-membered ring lactam **12** and the spirocyclic lactam **13**. Diastereomers **12** and **14** have near equivalent stabilities, but radical reduction from the β-face is blocked by the presence of the adjacent benzyloxycarbonyl substituent. The formation of **20** from **19**, by way of a disfavored 5-*endo-trig* cyclization pathway may have value as a model for synthesis of kopsinine-type alkaloids. The conversion of **8** to the functionalized hexahydrojulolidine **23** also is described.

Introduction

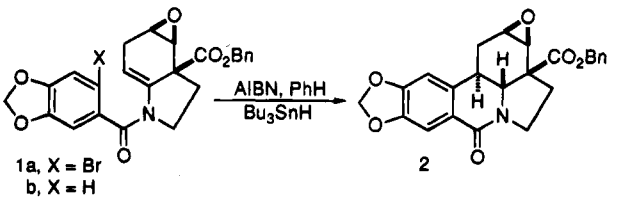
Several examples of radical cyclization to the enamide double bond have been reported in the last few years.[1,2] Most studies have focused on cyclizations of type A in which the nitrogen atom is exo to a ring containing the double bond[1a–f,h,i] and type B in which the nitrogen atom is within a ring containing the double bond.[1g]



Type A and B substrates have different conformational requirements for cyclization, especially the relative orientation of the olefin and carbonyl groups. Comparisons of rates of amide bond rotation and lifetimes of aryl radicals have shown that the geometry of an amide bond should be fixed during the lifetime of an aryl radical.[3] In general, 5-*exo-trig* are preferred over 6-*endo*-trig cyclizations in substituted hexenyl systems,[4] although a strong preference for 6-*endo-trig* cyclization has been observed[1b,f,i] for type A enamides; *e.g.*, **1a** → **2**. Facial selectivities of enamide–radical cyclizations of type B as a function of substituents at C(2) have been examined;[1g] except for our own study,[1f] investigations of possible facial selectivities of type A cyclizations have not been reported.[1j]

Treatment of enamide **1a** with AIBN and Bu_3SnH in refluxing benzene solution gave lactam **2** in 53% yield.[1f] The only other material isolated was the uncyclized product of reduction, **1b** (45%). Although **1b** may be formed by way of an intramolecular α-amidoyl to aryl 1,5-hydrogen atom transfer followed by reduction,[3] this possibility was not scrutinized by isotopic labeling experiments.

Molecular modeling of the radical derived from **1a** revealed that β-facial selectivity is a result of more favorable orbital overlap in the transition state for cyclization as well as a steric interaction that would result from passage of *pro*-C(14) near the C(15)–H bond during α-facial attack. Trans-dihydro stereochemistry in **2** (overall cis-addition) is reflective of the overwhelming stability of **2** (~11 kcal/mol) compared to the cis-dihydro product. Thus, the intermediate tertiary radical has geometry at C(16) analogous to that of **2**, and formation of the cis-isomer during reduction with Bu_3SnH is impossible because of excessive ring strain.[5]



The conversion of enamide **1a** to lactam **2** was utilized in the first asymmetric synthesis of a lycorine alkaloid.[1f] It is expected that analogous stereocontrolled radical addition reactions will find utility in alkaloid synthesis. In this paper, we describe the asymmetric synthesis and reactivity of four additional enamide systems and discuss

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1995.

(1) (a) Ishibashi, H.; Nakamura, N.; Sato, T.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett.* **1991**, *32*, 1725. (b) Rigby, J. H.; Qabar, M. *J. Am. Chem. Soc.* **1991**, *113*, 8975. (c) Sato, T.; Machigashira, N.; Ishibashi, H.; Ikeda, M. *Heterocycles* **1992**, *33*, 139. (d) Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2399. (e) Rigby, J. H.; Qabar, M. N. *J. Org. Chem.* **1993**, *58*, 4473. (f) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 7904. (g) Beckwith, A. L. J.; Joseph, S. P.; Mayadunne, T. A. *J. Org. Chem.* **1993**, *58*, 4198. (h) Fidalgo, J.; Castedo, L.; Dominguez, D. *Tetrahedron Lett.* **1993**, *34*, 7317. (i) For a subset of type A radical cyclizations, utilized for construction of the protoberberine ring system, see: Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Tetrahedron Lett.* **1990**, *31*, 2315. (j) However, for the utilization of (*R*)-1-methylbenzylamine to construct a chiral type A enamide, see ref 1i; little diastereoselectivity of undertermined absolute configuration was observed in the radical cyclization of the chiral enamide.

(2) For β-lactam construction by 4-*exo-trig* cyclization of acyclic enamides, see: Ishibashi, H.; Kameoka, C.; Iriyama, H.; Kodama, K.; Sato, T.; Ikeda, M. *J. Org. Chem.* **1995**, *60*, 1276.

(3) (a) Cohen, T.; McMullen, C. H.; Smith, K. *J. Am. Chem. Soc.* **1968**, *90*, 6866. (b) Snieckus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896.

(4) (a) Curran, D. P. *Synthesis* **1988**, 417. (b) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553.

(5) Schultz, A. G. *J. Chinese Chem. Soc. (Taiwan)* **1994**, *41*, 487.

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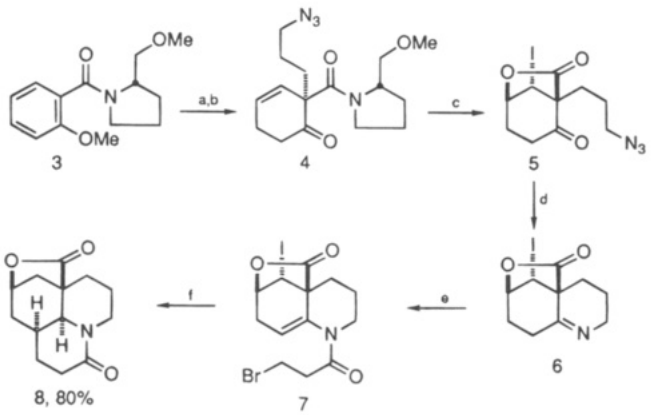
Scheme 1[a]



[a] Reagents: (a) K, NH_3, *t*-BuOH, THF, −78 °C; $N_3(CH_2)_3I$ (88%); (b) 6 N HCl, MeOH (82%); (c) I_2, THF, H_2O (95%); (d) PPh_3, THF, reflux (44%); or (i) $SnCl_2$, dioxane/H_2O; (ii) $NaHCO_3$ (60%); (e) 3-bromopropionyl chloride, $NaHCO_3$, 0 °C (96%); (f) Bu_3SnH, AIBN, PhH, reflux (80%).

factors that appear to be responsible for facial selectivity and regio- and stereocontrol.

Results and Discussion

The preparation and radical cyclization of enamide **7** is shown in Scheme 1. This system was selected for study because of the relationship of the expected product of radical cyclization **8** to the hexahydrojulolidines[6] and the lycopodium alkaloids.[7]

Birch reduction of the chiral benzamide **3**,[8] followed by alkylation of the resulting enolate with 1-azido-3-iodopropane,[9] gave a single diastereomer of the corresponding 1,4-cyclohexadiene in 88% yield on a 23 g scale; enol ether hydrolysis provided the azido enone **4**. Iodolactonization of **4** gave **5** in 95% yield with the option for recovery and reutilization of the chiral auxiliary.

Treatment of **5** with triphenylphosphine in THF gave imine **6** in only 44% yield. It is noteworthy that this procedure had provided a highly efficient route to a fused 1-pyrroline ring system from an iodo lactone analogous to **5** containing an azidoethyl substituent;[1f] however, with the propyl azide **5**, reactivity of the iodo substituent was competitive with formation of the 1-piperidine ring. Reductive cyclization of **5** with $SnCl_2$[10] offered a more chemoselective and operationally simplified route to **6**.

Imine **6** was acylated with 3-bromopropionyl chloride in THF/$NaHCO_3$ at 0 °C to give the crystalline enamide **7** in 96% yield, free of products of elimination of HBr. Radical cyclization of **7** with AIBN and Bu_3SnH in refluxing benzene solution gave the crystalline lactam **8** in 80% isolated yield; a single-crystal X-ray structure determination provided the molecular structure of **8**.[11a] Although the facial selectivity for the cyclization **7** → **8** is the same as that for **1a** → **2**, reduction of the intermediate tertiary radical produces cis- rather than trans-dihydro stereochemistry.[11b]

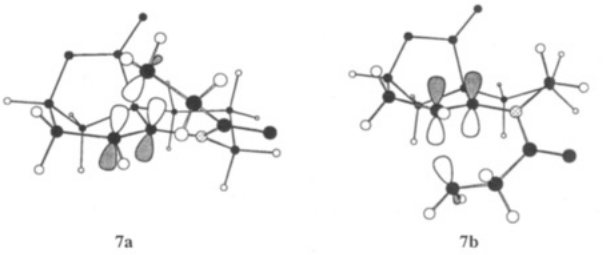
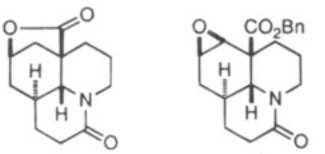


Figure 1. Transition state structures **7a** and **7b** for the radical cyclization of **7** showing a more favorable orbital overlap in **7a** compared to **7b**, along with a chair conformation for the piperidine ring in **7a** and a boat conformation in **7b**.

Facial selectivity for cyclization of the radical generated from **7** is assumed to be the result of kinetic control. Qualitative transition state structures for addition of the intermediate radical to either the β- or α-face of the enamide π−bond are shown in Figure 1. More favorable orbital overlap is possible in transition state structure **7a** that leads to **8** compared to that involved in α-facial attack, **7b**. Furthermore, the piperidine ring in **7a** is in a chair conformation while the piperidine ring in **7b** assumes the less stable boat conformation.[12]

Molecular modeling studies[12a] indicate that the trans-dihydro **9** isomer is 3.6 kcal/mol less stable than **8**. In analogy with the formation of **2**, the preferred pathway for reduction of the intermediate tertiary radical with Bu_3SnH correlates with product stability.



It was difficult to estimate the importance of the iodo lactone unit as a control element in the conversion of **7** to **8**. The timing of reduction of the iodo substituent in **7** is unknown, but on the basis of models taken from the literature probably occurs before radical cyclization.[13] Incorporation of a bridging lactone ring in **7** compared to the epoxide in **1a** results in an additional restriction of conformational mobility within the cyclohexene ring.

(6) For syntheses of the hexahydrojulolidines, see: Stevens, R. V. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1977; Vol. 3, pp 489−515.

(7) For syntheses of the lycopodium alkaloids, see: (a) Ayer, W. A.; Trifonov, L. S. In *The Alkaloids*; Cordell, G. A., Brossi, A., Eds.; Academic Press, Inc.: San Diego, CA, 1994; Vol. 45., p 233. (b) MacLean, D. B. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, p 241.

(8) (a) Schultz, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828. (b) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207. (c) Benzamide **3** is prepared by procedures described in ref 8a or may be purchased from Aldrich Chemical Co. (34,836−8).

(9) (a) Khoukhi, M.; Vaultier, M.; Carrie, R. *Tetrahedron Lett.* **1986**, *27*, 1031. (b) Conrad, P. C.; Kwiatkowski, P. L.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 586.

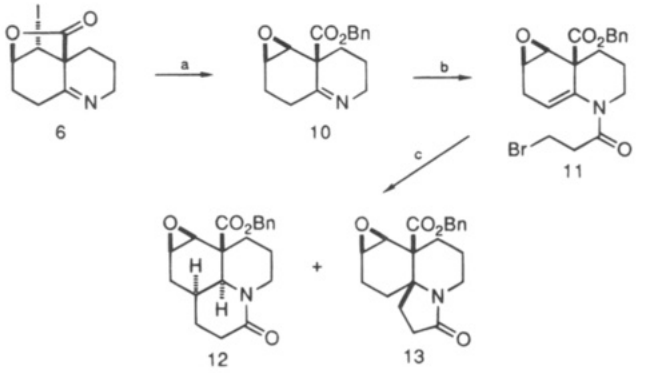
(10) (a) Maiti, S. N.; Singh, M. P.; Micetich, R. G. *Tetrahedron Lett.* **1986**, *27*, 1423. (b) Hendry, D.; Hough, L.; Richardson, A. C. *Tetrahedron Lett.* **1987**, *28*, 4597; these workers found that with $SnCl_2$ it was possible to selectively reduce an alkyl azide to an amine in the presence of a bromo substituent. (c) Evans, D. A.; Evrard, D. A.; Rychnovsky, S. D.; Früh, T.; Whittingham, W. G.; DeVries, K. M. *Tetrahedron Lett.* **1992**, *33*, 1189.

(11) (a) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallgraphic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K. (b) For an alternative route to cis-fused lactams via "aza-annulation" of *N*-acryloyl enamines followed by olefin hydrogenation, see: Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 1613 and references cited therein.

(12) (a) Molecular modeling studies were carried out with Macro-Model (MM2, Version 3.0). (b) It was found that the enacetamide analogue of **7a** (see structure **21**) is 1.2 kcal/mol more stable than that of **7b**.

(13) Ingold, K. U.; Lusztyk, J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 343.

Scheme 2[a]



[a] Reagents: BnOLi, THF, (84%); (b) 3-bromopropionyl chloride, $NaHCO_3$, 0 °C (42%); (c) Bu_3SnH, AIBN, PhH, reflux.

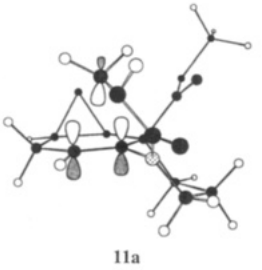


Figure 2. Transition state structure **11a** for the radical cyclization of **11**. The benzyl ester was replaced by a methyl ester for simplified molecular modeling and a hydrogen atom α to the amide carbonyl group was removed for clarity.

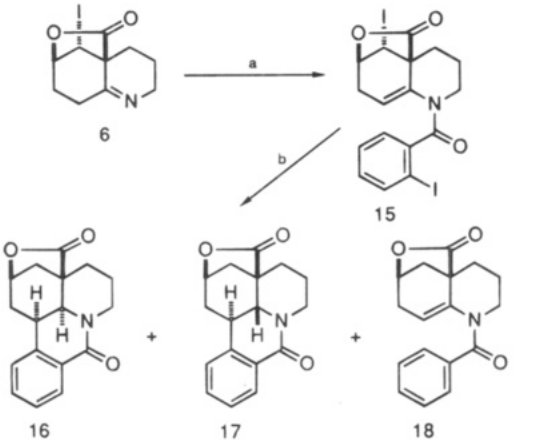
Epoxy enamide **11** was prepared to investigate the importance of the iodo lactone unit in **7** (Scheme 2). In contrast to **7**, radical cyclization of **11** gave a 1:1 mixture of the six-membered-ring lactam **12** and the spirocyclic lactam **13**. The assignment of cis-dihydro stereochemistry to **12** is supported by an observed coupling constant $J_{7a,10b}$ of 4.9 Hz, calculated 4.1 Hz.[12] Molecular modeling demonstrated that the trans-dihydro isomer **14** has nearly equivalent stability; $J_{7a,10b} = 11.4$ Hz. Presumably **14** is not formed under these reaction conditions because of steric effects of the adjacent benzyloxycarbonyl substituent (*vide infra*).

The structure of the spirocyclic lactam **13** was assigned on the basis of NMR spectral data and IR absorption at 1670 cm^{-1}, about 40 cm^{-1} higher energy than the lactam carbonyl stretching frequencies for **8** and **12**. The diastereomer of **13** that would have been produced by α-facial attack has considerable ring strain and is not formed to any detectable extent.

The absence of the bridging lactone ring characteristic of transition state structures **7a** and **7b** allows the epoxy-1,4-cyclohexadiene ring in **11a** to assume a planar conformation (Figure 2).[14] It would appear that cyclization to either **12** or **13** can occur with equal facility from this transition state representation.

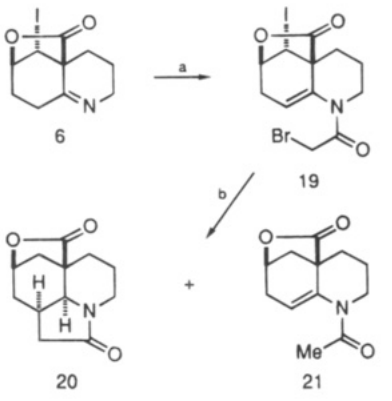
MM2 calculations[12a] indicate that **16**, the benzoannelated analogue of **8**, is only 1.8 kcal/mol more stable than the trans-dihydro isomer **17**. Radical cyclization of aryl iodide **15** (Scheme 3) with Ph_3SnH gave a mixture of **16** (62%), **17** (22%), and the uncyclized reduction product **18** (13%). Utilization of Bu_3SnH in the cyclization

Scheme 3[a]



[a] Reagents: (a) 2-iodobenzoyl chloride, Et_3N, THF (92%); (b) Ph_3SnH, AIBN, PhH, reflux.

Scheme 4[a]



[a] Reagents: (a) bromoacetyl chloride, $NaHCO_3$, THF (70%); (b) Bu_3SnH, AIBN, PhH, reflux.

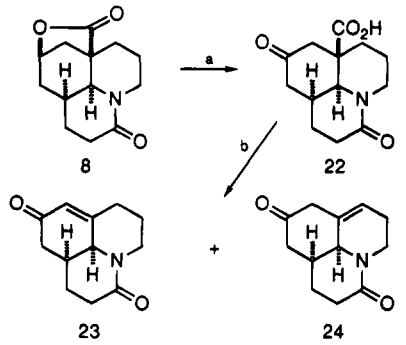
resulted in a reduced ratio of *cis*-**16** to *trans*-**17** (1.8 vs 2.8). Presumably, the increased steric bulk of Ph_3SnH is responsible for greater facial discrimination in the hydrogen atom transfer step. Compared to the conversion of **1a** to **2**, the efficiency of cyclization (relative to reduction of the aryl radical) is greater with the enlarged nitrogen containing ring in **15**, although the attendant loss of a large ring strain difference between **16** and **17** results in less stereoselectivity for reduction of the intermediate tertiary radical.

As would be anticipated from the discussion of facial selectivity for the conversion of **7** to **8** (cf. transition state structure **7a**), radical cyclization of α-bromoacetamide **19** (Scheme 4) proved to be completely β-facial selective to give cis-dihydro **20** in 63% yield. Molecular modeling demonstrated that **20** is 8.5 kcal/mol more stable than the corresponding trans isomer (not shown), completely in accord with the rationale for stereocontrol developed for the radical reduction pathways to **2** and **8**. The formation of **20** by way of a "disfavored" 5-*endo-trig* cyclization[15] has precedence in the studies of Ikeda and co-workers.[1a] None of the β-lactam derivative that would have been produced by a 4-*exo-trig* cyclization[2] was

(14) An epoxy-1,4-cyclohexadiene has been found to be planar by X-ray structure determination; see: Schultz, A. G.; Harrington, R. E.; Tham, F. S. *Tetrahedron Lett.* **1992**, *33*, 6097.

(15) (a) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736. (b) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482. (c) Mendenhall, G. D.; Protasiewicz, J. D.; Brown, C. E.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1994**, *116*, 1718.

Scheme 5[a]



[a] Reagents: (a) (i) 1 M KOH, THF; (ii) aqueous Na_2RuO_4; (iii) H^+ (46%); (b) $Pb(OAc)_4$, CH_3CN (50%).

observed. We note that 5-*endo-trig* cyclizations of C(8)-aryl-substituted analogues of **19** may have value in the synthesis of kopsinine-type alkaloids.[16]

The conversion of **8** to the functionalized hexahydrojulolidines **23** and **24** is shown in Scheme 5. Saponification of lactone **8** with KOH in THF solution was followed by direct treatment with sodium ruthenate.[17] The resulting keto acid **22** was subjected to oxidative decarboxylation[18] with $Pb(OAc)_4$ in CH_3CN and photolysis at 366 nm to give a 4:1 mixture of enones **23** and **24**. Chromatography on silica gel or treatment of the mixture with silica gel in CH_2Cl_2 resulted in conjugation of **24** to give **23** free from epimerization to the corresponding trans-dihydro isomer (not shown).

Conclusion

Complete facial selectivity has been observed for chiral enamide radical cyclizations of type A ($n = 2$) when the nitrogen atom is contained in an annelated pyrrolidine or piperidine ring to give bis-annelated five- and six-membered lactams. Stereoelectronic arguments[19] have provided effective explanations for facial control. The stereoselectivity for reduction of the intermediate tertiary radicals with Bu_3SnH correlates with product stability, although steric effects may exert significant control when diastereomeric products have similar stabilities (*e.g.*, **11** → **12**). It is expected that this perhaps under-recognized feature of the stereoselectivity of radical reduction will have broad application; it should be possible to predict the stereoselectivity for radical reduction in related ring systems by judicious molecular modeling. Finally, the bridging lactone in **7** was found to exert significant regiocontrol in the radical cyclization to **8**; cf. **11** → **12** + **13**.

Experimental Section

(2′*S*,2*R*)-2-(3-Azidopropyl)-2-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-3-cyclohexen-1-one (4). A 3 L flask equipped with a dry ice condenser, overhead stirrer, and drying tube was charged with **2** (18.26 g, 77.6 mmol), dry THF (250 mL), and *t*-BuOH (7.32 mL, 77.6 mmol). The solution was cooled to −78 °C under N_2, and ~1 L of NH_3 was added. Potassium (~9 g) was added until a blue color remained. The solution was stirred at −78 °C for 30 min after which piperylene (~0.5 mL) was added dropwise until a color change from blue to yellow occurred. 1-Azido-3-iodopropane[9b] (26.77 g, 127 mmol) was added, and the solution was stirred at −78 °C for 3 h. NH_4Cl was added, the ice bath and condenser were removed, and the NH_3 was allowed to evaporate overnight under a stream of N_2. The residue was extracted from H_2O (1500 mL) with CH_2Cl_2 (1500 mL). The organic layer was then washed sequentially with 10% HCl, $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated to give the intermediate 1,4-cyclohexadiene (22.88 g, 88%) as a yellow oil. Due to the instability of the 1,4-cyclohexadiene upon storage, it was used in the next step shortly after workup. TLC $R_f = 0.48$ (30% EtOAc in hexane, I_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.91 (dt, 1 H, $J = 9.8$, 3.1 Hz), 5.35 (dt, 1 H, $J = 9.8$, 2.0 Hz), 4.80 (m, 1 H), 4.30 (m, 1 H), 3.74 (m, 1 H), 3.61 (dm, 1 H, $J = 9.5$ Hz), 3.52 (s, 3 H), 3.34 (s, 3 H), 3.26 (m, 3 H), 2.92 (dm, 1 H, $J = 19.5$ Hz), 2.81 (dm, 1 H, $J = 19.5$ Hz), 2.11 (dt, 1 H, $J = 4.7$, 13.2 Hz), 1.6−1.9 (m, 6 H), 1.50 (m, 1 H), 1.39 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.9, 152.6, 126.3, 126.2, 92.9, 71.8, 67.7, 58.7, 58.0, 54.0, 51.6, 45.8, 33.0, 26.6, 26.1, 24.7, 23.3; IR (film) 2100, 1630 cm^{-1}; $[\alpha]^{30}_D = -32.9°$ (*c* 1.08, $CHCl_3$).

A solution of the 1,4-cyclohexadiene (22.71 g, 0.068 mol), MeOH (1 L), and 6 N HCl (250 mL) was stirred at room temperature for 18 h. The MeOH was evaporated under reduced pressure, and the residue was extracted into CH_2Cl_2. The organic layer was washed sequentially with $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated to give **4** as an amber oil (17.87 g, 82%): TLC $R_f = 0.43$ (1:1 EtOAc:hexane, I_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.02 (dm, 1 H, $J = 9.7$ Hz), 5.68 (d, 1 H, $J = 9.7$ Hz), 4.26 (m, 1 H), 3.63 (dd, 1 H, $J = 3.2$, 9.3 Hz), 3.36 (s, 3 H), 3.30 (m, 4 H), 3.08 (m, 1 H), 2.55 (m, 4 H), 2.03 (m, 1 H), 1.90 (m, 3 H), 1.75 (m, 1 H), 1.65 (m, 1 H), 1.59 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.6, 168.0, 129.0, 127.8, 71.6, 60.8, 58.9, 57.9, 51.5, 46.6, 36.5, 33.8, 33.7, 26.6, 25.9, 24.5; IR (film) 2100, 1705, 1620 cm^{-1}; $[\alpha]^{26}_D = -49.2°$ (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{16}H_{24}N_4O_3$: C, 59.98; H, 7.55; N, 17.49. Found: C, 59.74; H, 7.57; N, 17.49.

(2*R*,3*R*,4*R*)-1-Oxo-2-(3-azidopropyl)-3-iodocyclohexane-2,4-carbolactone (5). I_2 (84.9 g, 0.33 mol) was added to a solution of **4** (17.87 g, 0.056 mol) in THF:H_2O (1:1, 600 mL). The reaction mixture was stirred at room temperature for 24 h and then titrated with saturated $Na_2S_2O_3$ until the color of the solution changed from brown to yellow. The THF was removed in vacuo, and the residue was extracted into CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give **5** (18.43 g, 95%) as a light brown oil which solidified upon standing: recrystallization from EtOAc and hexane; mp 51−52 °C; TLC $R_f = 0.54$ (1:1 EtOAc:hexane, I_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.03 (m, 1 H), 4.78 (dd, 1 H, $J = 1.7$, 5.4 Hz), 3.33 (m, 2 H), 2.62 (m, 3 H), 2.45 (m, 1 H), 1.94 (m, 1 H, $J = 11.7$ Hz), 1.79 (m, 1 H, $J = 11.7$ Hz), 1.46 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.7, 169.3, 63.1, 51.1, 51.0, 32.9, 27.1, 23.3, 22.4, 22.2; IR (film) 2100, 1785, 1720 cm^{-1}; CI-MS *m/z* (relative intensity) 350 ($M^+ + 1$, 38), 322 (50), 196 (58), 150 (100); $[\alpha]^{26}_D = -144.8°$ (*c* 1.19, $CHCl_3$). Anal. Calcd for $C_{10}H_{12}IN_3O_3$: C, 34.40; H, 3.46; N, 12.04. Found: C, 34.37; H, 3.33; N, 11.96.

(4a*R*,5*R*,6*R*)-5-Iodo-2,3,7,8-tetrahydro-4*H*-quinoline-4a,6-carbolactone (6). To a solution of **5** (1.05 g, 3.01 mmol) in THF (30 mL) was added PPh_3 (860 mg, 3.28 mmol). After 3.5 h of reflux, the solvent was evaporated; flash chromatography (silica gel, 1:3 EtOAc:hexane) gave **6** (408 mg, 44%) as a white solid.

Alternative Procedure. **5** (200 mg, 0.573 mmol) was added to a solution of $SnCl_2$ (380 mg, 2.01 mmol) in dioxane (2.0 mL) and H_2O (1.0 mL) under nitrogen, which produced an immediate slow evolution of N_2. The solution was stirred for 7 h at room temperature; then dioxane (1.0 mL) and H_2O (1.0 mL) were added followed by $NaHCO_3$ (385 mg, 4.58 mmol). A white precipitate formed, and the resulting mixture was stirred for 45 min, then filtered, and washed with CH_2Cl_2. The

(16) Thomas, D. W.; Achenbach, H.; Biemann, K. *J. Am. Chem. Soc.* **1966**, *88*, 1537.

(17) (a) Lee, D. G.; Hall, D. T.; Cleland, J. H. *Can. J. Chem.* **1972**, *50*, 3741. (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8034. (c) Gopal, H.; Adams, T.; Moriarty, R. *Tetrahedron* **1972**, *28*, 4259.

(18) (a) McMurry, J. E.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39*, 2217. (b) Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 4321.

(19) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1984.

organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and evaporated. Flash chromatography (silica gel, 1:1 EtOAc:hexane) gave 105 mg (60%) of **6** as a white solid: mp 123–124.5 °C; TLC R_f = 0.29 (1:1 EtOAc:hexane, I_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.88 (m, 1 H, J = 5.2, 3.4 Hz), 4.49 (dd, 1 H, J = 5.2, 1.7 Hz), 3.71 (dm, 1 H, J = 17.3 Hz), 3.52 (m, 1 H, J = 17.3 Hz), 2.69 (m, 1 H, J = 14.7, 7.8 Hz), 2.58 (dd, 1 H, J = 7.8, 16.9 Hz), 2.50 (m, 1 H, J = 16.9 Hz), 2.39 (m, 1 H, J = 1.7, 14.7 Hz), 2.19 (m, 1 H, J = 14.4 Hz), 1.85 (m, 2 H), 1.69 (m, 1 H, J = 14.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.4, 160.3, 78.2, 50.6, 48.5, 30.0, 29.4, 26.0, 25.4, 19.0; IR (film) 1780, 1660 cm^{-1}; CI-MS m/z (relative intensity) 306 (M^+ + 1, 100), 178 (26); $[\alpha]^{25}_D$ = −206.2° (c 1.04, $CHCl_3$). Anal. Calcd for $C_{10}H_{12}INO_2$: C, 39.37; H, 3.96; N, 4.59. Found: C, 39.39; H, 3.83; N, 4.45.

(4a*R*,5*R*,6*R*)-*N*-(3-Bromopropionyl)-5-iodo-2,3-dihydro-4*H*,7*H*-quinoline-4a,6-carbolactone (7). A mixture of **6** (206 mg, 0.676 mmol) and $NaHCO_3$ (85 mg, 1.014 mmol) in THF (20 mL) was cooled to 0 °C. 3-Bromopropionyl chloride (68 μL, 0.676 mmol) was added, and the solution was stirred at 0 °C for 3 h. The solvent was evaporated, and the residue was partitioned between CH_2Cl_2 and H_2O. The aqueous layer was washed three times with CH_2Cl_2, and the pooled organic extracts were evaporated to give **7** (285 mg, 96%) as an off-white solid: recrystallization from EtOAc and hexane; mp 154–155 °C dec; TLC R_f = 0.43 (1:1 EtOAc:hexane, I_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.60 (br s, 1 H), 4.74 (m, 1 H, J = 5.1, 2.9, 2.2 Hz), 4.48 (d, 1 H, J = 5.1 Hz), 3.97 (m, 1 H, J = 12.4 Hz), 3.70 (m, 1 H, J = 5.8, 6.9 Hz), 3.58 (m, 1 H, J = 8.1, 5.4 Hz), 3.43 (m, 1 H, J = 5.1, 5.1, 4.9 Hz), 3.15 (m, 1 H, J 15.8, 5.8, 8.1 Hz), 3.09 (ddd, 1 H, J = 2.7, 19.5, 2.9 Hz), 2.82 (m, 1 H, J = 15.8, 6.9, 5.4 Hz), 2.76 (ddd, 1 H, J = 2.2, 19.5, 3.9 Hz), 2.10 (m, 2 H), 1.97 (m, 1 H), 1.83 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.3, 170.1, 117.2, 94.7, 75.8, 67.9, 46.9, 43.0, 35.8, 30.1, 27.6, 25.6, 25.5, 23.9, 19.2; IR (CH_2Cl_2) 1775, 1640 cm^{-1}; CI-MS m/z (relative intensity) 442 (M^+ + 1, 30), 440 (30), 396 (12), 360 (12), 316 (100), 314 (100), 270 (70), 234 (100); [α] = +181.1° (c 1.48, $CHCl_3$). Anal. Calcd for $C_{13}H_{15}BrINO_3$: C, 35.48; H, 3.44; N, 3.18. Found: C, 35.81; H, 3.40; N, 3.16.

(7a*R*,9*R*,10a*R*,10b*S*)-2,3,6,7,7a,10b-Hexahydro-1*H*,8*H*,-10*H*-5-oxobenzo[*ij*]quinolizine-10a,9-carbolactone (8). A solution of **7** (210 mg, 0.477 mmol), n-Bu_3SnH (320 μL, 1.19 mmol), and AIBN (8 mg, 0.048 mmol) in benzene (40 mL) was degassed by bubbling N_2 into the solution for 15 min. After 5 h of reflux, another 0.1 equiv of AIBN was added if the reaction was judged incomplete by TLC. Chromatography on silica gel (1–2% MeOH in CH_2Cl_2) gave **8** (91 mg, 80%) as a white solid: recrystallization from CH_2Cl_2 and hexane; mp 184–185 °C; TLC R_f = 0.47 (10% MeOH in CH_2Cl_2, I_2); ^{1}H NMR (C_6D_6, 500 MHz) δ 5.12 (m, 1 H, J = 13.0 Hz), 3.87 (m, 1 H, J = 1.5 Hz), 4.48 (d, 1 H, J = 5.1 Hz), 2.54 (d, 1 H, J = 7.5 Hz), 2.40 (m, 1 H, J = 13.0 Hz), 2.37 (m, 1 H, J = 17.5 Hz), 2.06 (ddd, 1 H, J = 4.5, 13.5, 18.0 Hz), 1.90 (ddd, 1 H, J = 13.0, 15.0, 2.5 Hz), 1.81 (m, 1 H, J = 17.5 Hz), 1.52 (m, 1 H, J = 8.5, 7.5), 1.45 (m, 1 H, J = 12.5 Hz), 1.33 (ddd, 1 H, J = 2.0, 6.0, 11.5 Hz), 1.26 (m, 1 H, J = 2.0, 15.0 Hz), 1.11 (m, 1 H, J = 13.0 Hz), 1.01 (ddd, 1 H, J = 1.5, 8.5, 15.0), 0.87 (m, 1 H, J = 13.5 Hz), 0.81 (ddd, 1 H, J = 5.0, 13.5, 13.5 Hz), 0.58 (d, 1 H, J = 11.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.5, 168.5, 74.7, 61.9, 43.4, 42.9, 42.7, 34.0, 32.9, 31.2, 30.7, 27.0, 21.4; IR (film) 1775, 1630 cm^{-1}; CI-MS m/z (relative intensity) 236 (M^+ + 1, 100); $[\alpha]^{22}_D$ +30.9° (c 1.1, $CHCl_3$). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 65.96; H, 7.27; N, 5.86. Diagnostic NOESY data (C_6D_6, 500 MHz) for determination of stereochemistry at C(10b) and C(7a):

proton	NOE interaction	distance, Å (Macromodel)
10b (2.54 ppm)	10ax (0.58 ppm)	2.4
	1ax (0.81 ppm)	2.7
	3ax (1.90 ppm)	2.5

All four possible diastereomers from radical cyclization were modeled and minimized using Macromodel. **8**, $J_{H10b-H7a}$ observed = 7.5 Hz. The calculated Macromodel data: $J_{H10b\alpha-H7a\alpha}$ = 6.8 Hz, 14.7 kcal/mol; $J_{H10b\alpha-H7a\beta}$ = 11.2 Hz, 11.2 kcal/mol; $J_{H10b\beta-H7a\beta}$ = 5.6 Hz, 13.1 kcal/mol; $J_{H10b\beta-H7a\alpha}$ = 11.0 Hz, 18.3 kcal/mol.

(4a*R*,5*S*,6*R*)-5,6-Epoxy-2,3,7,8-tetrahydro-4*H*-4a-(benzyloxycarbonyl)quinoline (10). To dry benzyl alcohol (0.16 mL, 1.52 mmol) in 3 mL of THF at 0 °C was added n-BuLi (2.5M in hexane, 0.32 mL, 0.79 mmol). After stirring for 15 min, the solution was cooled to −78 °C and a solution of **6** (210 mg, 0.69 mmol) in THF (3 mL) was added. The solution was stirred overnight with warming to room temperature. Saturated NH_4Cl was added and the THF evaporated. The residue was extracted into CH_2Cl_2, dried over Na_2SO_4, and concentrated. Flash chromatography (silica gel, EtOAc) gave **10** (164 mg, 84%) as a yellow oil: TLC R_f = 0.21 (EtOAc, I_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37 (m, 5 H), 5.24 (s, 2 H), 3.75 (dd, 1 H, J = 18.5, 5.4 Hz), 3.51 (m, 1 H, J = 18.5), 3.37 (m, 1 H, J = 3.6 Hz), 3.18 (d, 1 H, J = 3.6 Hz), 2.63 (m, 1 H, J = 4.7, 10.7, 12.7 Hz), 2.44 (m, 1 H, J = 4.7, 13.7 Hz), 2.31 (m, 1 H), 2.15 (dd, 1 H, J = 4.9, 12.7, Hz), 1.98 (ddd, 1 H, J = 4.9, 10.7, 13.7 Hz), 1.70 (m, 1 H), 1.62 (m, 1 H), 1.52 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.1, 164.9, 135.4, 128.3, 128.0, 127.7, 66.8, 56.8, 53.3, 48.53, 47.1, 30.1, 28.2, 25.5, 18.9; IR (film) 1725, 1655 cm^{-1}; CI-MS m/z (relative intensity) 286 (M^+ + 1, 100); $[\alpha]^{25}_D$ = −190.0° (c 1.04, $CHCl_3$); HRMS (M^+ + 1) calcd for $C_{17}H_{19}NO_3$ 286.1443, found 286.1440.

(4a*R*,5*S*,6*R*)-*N*-(3-Bromopropionyl)-5,6-epoxy-2,3-dihydro-4*H*,7*H*-10a-(benzyloxycarbonyl)quinoline (11). To a solution of **10** (101 mg, 0.354 mmol) in THF (14 mL) at 0 °C were added $NaHCO_3$ (59 mg, 0.708 mmol) and 3-bromopropionyl chloride (38 μL, 0.372 mmol). After 2.5 h, the mixture was diluted with 20 mL of H_2O and extracted with CH_2Cl_2. The pooled organic layers were dried over Na_2SO_4, filtered, and evaporated. Flash chromatography (silica gel, EtOAc/hexane, 3:2) gave **11** (79 mg, 42%) (R_f = 0.54, EtOAc, I_2) as a colorless oil. Due to the instability of **11** upon storage (loss of HBr), it was used in the next step shortly after chromatography: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (m, 5 H), 5.52 (m, 1 H, J = 3.4, 3.6 Hz), 5.21 (s, 2 H), 4.73 (dd, 1 H, J = 4.4, 12.7 Hz), 3.69 (m, 1 H), 3.39 (m, 2 H, J = 3.4, 3.7 Hz), 3.31 (d, 1 H, J = 3.7 Hz), 3.08 (m, 1 H), 3.02 (m, 1 H), 2.84 (dd, 1 H, J = 3.4, 20.3 Hz), 2.62 (ddd, 1 H, J = 3.4, 3.6, 20.3 Hz), 2.56 (m, 2 H, J = 12.7 Hz), 1.73 (m, 1 H), 1.65 (m, 1 H), 1.56 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 169.7, 135.3, 135.0, 128.6, 128.4, 128.2, 120.0, 67.2, 56.9, 50.4, 48.1, 44.6, 37.3, 36.0, 33.7, 28.3, 25.1, 22.6; IR (film) 1735, 1640 cm^{-1}; $[\alpha]^{24}_D$ = +121.2° (c 0.73, $CHCl_3$); CI-MS m/z (relative intensity) 422 (M^+ + 1, 40), 420 (M^+ + 1, 40), 340 (100).

(7a*S*,9*R*,10*S*,10a*R*)-2,3,6,7,7a,10b-Hexahydro-1*H*,8*H*-5-oxo-9,10-epoxy-10a-(benzyloxycarbonyl)benzo[*ij*]quinolizine (12) and (7a*S*,8*S*,9*R*,11a*S*)-1,2,5,6,10,11-Hexahydro-7*H*-3-oxo-7a-(benzyloxycarbonyl)-8,9-epoxypyrrolo[2,1-*j*]quinoline (13). A solution of **11** (56 mg, 0.133 mmol), n-Bu_3SnH (42 μL, 0.159 mmol), and AIBN (2.4 mg, 0.015 mmol) in benzene (10 mL) was degassed by bubbling N_2 into the solution for 15 min. The solution was refluxed overnight under N_2, then cooled, and concentrated under reduced pressure. An ^{1}H NMR spectrum of the residue showed a 1:1 mixture of **12**:**13**. Column chromatography (silica gel, EtOAc) gave 8.5 mg (19%) of **13** (R_f = 0.25, EtOAc, phosphomolybdic acid stain) as an oil, 16 mg (35%) of a mixture of **12** and **13**, and 16.5 mg (36%) of a mixture enriched in **12** as a white solid. Pure **12** was obtained by crystallization from EtOAc: mp 220–223 °C dec; TLC R_f = 0.20 (EtOAc, phosphomolybdic acid stain); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (m, 5 H), 5.20 (d, 1 H, J = 12.5 Hz), 5.16 (d, 1 H, J = 12.5 Hz), 4.71 (dd, 1 H, J = 5.1, 13.2 Hz), 3.31 (m, 1 H), 3.16 (d, 1 H, J = 3.4 Hz), 3.09 (d, 1 H, J = 4.9 Hz), 2.58 (dt, 1 H, J = 4.1, 12.9 Hz), 2.52 (dd, 1 H, J = 6.3, 17.6 Hz), 2.39 (dm, 1 H, J = 13.7 Hz), 2.31–2.25 (m, 3 H), 2.24–2.18 (m, 1 H), 2.14 (d, 1 H, J = 15.8 Hz), 2.08–2.01 (m, 1 H), 1.72 (dt, 1 H, J = 3.9, 13.4 Hz), 1.63–1.51 (m, 3 H); ^{13}C ($CDCl_3$, 125 MHz) δ 171.4, 169.8, 135.9, 128.5, 128.17, 128.14, 66.3, 61.2, 56.5, 54.1, 45.7, 42.9, 36.3, 32.9, 29.8, 27.9, 26.4, 22.5; IR ($CHCl_3$) 1740, 1630 cm^{-1}; CI-MS m/z (relative intensity) IBCI MH^+ 342 (M^+ + 1, 100); $[\alpha]^{25}_D$ = +52° ($CHCl_3$, c 1.01); HRMS (M^+ + 1) calcd for $C_{20}H_{23}NO_4$ 342.1705, found

342.1707. Diagnostic NOESY data ($CDCl_3$, 500 MHz) for determination of stereochemistry at C(10b) and C(7a):

proton	NOE interaction	distance, Å (Macromodel)
10b (3.09 ppm)	3ax (2.58 ppm)	2.5
	1ax (1.72 ppm)	2.3

All four possible diastereomers from radical cyclization were minimized and modeled using Macromodel. **12**, $J_{H10b-H7a}$ observed = 4.9 Hz. The calculated Macromodel data: $J_{H10b\alpha-H7a\alpha}$ = 4.1 Hz, 26.6 kcal/mol; $J_{H10b\alpha-H7a\beta}$ = 10.9 Hz, 21.1 kcal/mol; $J_{H10b\beta-H7a\beta}$ = 2.1 Hz, 22.5 kcal/mol; $J_{H10b\beta-H7a\alpha}$ = 11.4 Hz, 26.4 kcal/mol. **13**: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.35 (m, 5 H), 5.25 (d, 1 H, J = 12.2 Hz), 5.16 (d, 1 H, J = 12.2 Hz), 4.15 (dm, 1 H, J = 13.0 Hz), 3.41 (d, 1 H, J = 3.6 Hz), 3.22 (m, 1 H, J = 3.6 Hz), 2.71 (dt, 1 H, J = 4.4, 13.1 Hz), 2.29–2.20 (m, 3 H), 2.16–2.09 (m, 2 H), 2.08–2.00 (m, 1 H), 1.95 (dd, 2 H, J = 3.9, 9.3 Hz), 1.88–1.82 (m, 1 H), 1.64–1.51 (m, 2 H), 1.12 (dd, 1 H, J = 4.6, 12.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.7, 172.3, 135.6, 128.68, 128.48, 128.43, 66.7, 61.5, 59.5, 51.6, 49.1, 35.3, 29.9, 28.3, 27.9, 27.8, 20.6, 19.9; IR (CH_2Cl_2) 1725, 1670 cm^{-1}; CI-MS m/z (relative intensity) 342 (M^+ + 1, 100); $[\alpha]^{23}_D$ = −15.0° ($CHCl_3$, c 1); HRMS (M^+ + 1) calcd for $C_{20}H_{23}NO_4$ 342.1705, found 342.1702.

(4a*R*,5*R*,6*R*)-*N*-(2-Iodobenzoyl)-5-iodo-2,3-dihydro-4*H*,7*H*-quinoline-4a,6-carbolactone (15). 2-Iodobenzoic acid (187 mg, 0.752 mmol) was dissolved in 1.5 mL of thionyl chloride and refluxed for 2 h. Excess thionyl chloride was removed by evaporation to give the acid chloride as a yellow solid. To a solution of the acid chloride in THF (10 mL) at 0 °C was added Et_3N (125 μL, 0.886 mmol) followed by **6** (225 mg, 0.738 mmol). The solution was warmed to room temperature and stirred overnight. The solvent was evaporated. The residue was dissolved in 75 mL of EtOAc and washed sequentially with 0.5 M HCl, saturated $NaHCO_3$, and brine. The organic layers were dried over Na_2SO_4, filtered, and evaporated to give 364 mg of an off white solid (92%). An analytical sample of **15** was obtained by recrystallization from refluxing EtOAc to give 296 mg (75%) of white crystals: mp 210–211 °C dec; TLC R_f = 0.46 (1:1 EtOAc:hexane, I_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.81 (d, 1 H, J = 7.8 Hz), 7.31 (m, 1 H), 7.05–6.99 (m, 2 H), 5.15 (br s, 1 H), 4.54 (m, 1 H), 4.40 (d, 1 H, J = 5.1 Hz), 4.32 (m, 1 H), 3.32 (m, 1 H), 2.80 (dm, 1 H, J = 18.8 Hz), 2.24 (m, 1 H), 2.06 (m, 2 H), 1.93 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1, 141.9, 139.3, 132.2, 130.0, 128.0, 126.1, 118.0, 95.2, 75.6, 46.5, 43.8, 30.1, 26.2, 25.2, 20.3, (note one C=O is missing); IR ($CHCl_3$) 1775, 1640 cm^{-1}; CI-MS m/z (relative intensity) 536 (M^+ + 1, 20), 410 (40), 282 (100), 238 (45); $[\alpha]^{22}_D$ = +210.6° (c 0.79, $CHCl_3$). Anal. Calcd for $C_{17}H_{15}I_2NO_3$: C, 38.16; H, 2.83; N, 2.62. Found: C, 37.85; H, 2.67; 2.57.

Radical Cyclization of 15. A solution of **15** (72 mg, 0.14 mmol), Ph_3SnH (113 mg, 0.322 mmol), and AIBN (2.5 mg, 0.015 mmol) in benzene (13 mL, c 0.01 M) was degassed by bubbling N_2 through the solution for 15 min. The solution was refluxed overnight under N_2, then cooled, and concentrated under reduced pressure. Column chromatography (silica gel, gradient elution from 1:1 EtOAc:hexane to EtOAc) gave 5 mg (13%) of **18** as an oil (R_f = 0.51, EtOAc, I_2), 8.2 mg (22%) of **17** (R_f = 0.44, EtOAc, I_2), and 23.5 mg (62%) of **16** (R_f = 0.28, EtOAc, I_2).

Alternative Procedure. A solution of **15** (55 mg, 0.10 mmol), Bu_3SnH (70 μL, 0.26 mmol), and AIBN (2.0 mg, 0.012 mmol) in benzene (7.0 mL) was treated under the conditions described above. Column chromatography gave 3.5 mg (12%) **18**, 7.7 mg (27%) **17**, and 14 mg (48%) of **16**.

(2*R*,3a*R*,12b*S*,12c*S*)-2,3,3a,5,6,8,12b,12c-Octahydro-8-oxo-1*H*,4*H*-pyrido[3,2,1-*de*]phenanthridine-3a,2-carbolactone (16): mp 246–248 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.15 (dd, 1 H, J = 1.2, 7.9 Hz), 7.47 (dt, 1 H, J = 1.2, 7.9 Hz), 7.34 (d, 1 H, J = 7.8 Hz), 7.31 (t, 1 H, J = 7.6 Hz), 4.94 (dm, 1 H, J = 12.9 Hz), 4.79 (t, 1 H, J = 5.5 Hz), 4.02–3.96 (m, 2 H, see ^1H in 1:1 $CDCl_3$:C_6D_6, listed next, for a first-order spectrum in this region), 3.18 (ddd, 1 H, J = 1.9, 4.9, 15.0 Hz), 2.68 (dt, 1 H, J = 2.5, 12.9 Hz), 2.33–2.13 (m, 2 H), 2.15 (dd, 1 H, J = 7.1, 15.0 Hz), 2.05–1.99 (dm, 1 H, J = 13.7 Hz), 1.82 (d, 1 H, J = 11.7 Hz), 1.68 (dd, 1 H, J = 4.6, 13.7 Hz), 1.63–1.59 (m, 1 H); ^1H NMR (1:1 $CDCl_3$:C_6D_6, 500 MHz) δ (expansion of region between 5 and 1 ppm used in conjunction with NOESY experiment for determination of stereochemistry) 4.89 (dm, 1 H, J = 12.5 Hz), 4.24 (t, 1 H, J = 5.3 Hz), 3.46 (t, 1 H, J = 7.8 Hz), 3.33 (d, 1 H, J = 8.3 Hz), 2.70 (ddd, 1 H, J = 2.1, 4.8, 15.1 Hz), 2.33 (dt, 1 H, J = 2.2, 12.5 Hz), 2.24 (tq, 1 H, J = 3.9, 13.2 Hz), 1.73–1.67 (m, 2 H), 1.50 (dd, 1 H, J = 7.3, 15.1 Hz), 1.34–1.29 (m, 1 H), 1.18 (dt, 1 H, J = 4.7, 13.2 Hz), 1.13 (d, 1 H, J = 11.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.3, 162.3, 137.3, 132.0, 128.6, 127.3, 126.9, 124.7, 74.1, 62.0, 45.9, 43.8, 43.2, 31.5, 30.3, 30.2, 21.7; IR ($CHCl_3$) 1770, 1640 cm^{-1}; $[\alpha]^{24}_D$ = +99.3° (c 1.4, $CHCl_3$); CI-MS m/z (relative intensity) 284 (M^+ + 1, 100); HRMS (M^+ + 1) calcd for $C_{17}H_{17}NO_3$ 284.1287, found 284.1287. Diagnostic NOESY data (1:1 $CDCl_3$:C_6D_6, 500 MHz) for determination of stereochemistry at C(12c) and C(12b):

proton	NOE interaction	distance, Å (Macromodel)
12c (3.33 ppm)	12b (3.46 ppm)	2.3
	6ax (2.33 ppm)	2.4
	3ax (1.13 ppm)	2.5
12b (3.46 ppm)	1ax (1.50 ppm)	2.4

All four possible diastereomers from radical cyclization were minimized and modeled using Macromodel. **14**, $J_{H12c-H12b}$ observed = 8.3 Hz; for product **15**, $J_{H12c-H12b}$ observed = 12 Hz. The calculated Macromodel data: $J_{H12c\alpha-H12b\alpha}$ = 6.2 Hz, 17.5 kcal/mol; $J_{H12c\alpha-H12b\beta}$ = 11.3 Hz, 15.6 kcal/mol; $J_{H12c\beta-H12b\beta}$ = 5.8 Hz, 13.9 kcal/mol; $J_{H12c\beta-H12b\alpha}$ = 10.5 Hz, 19.3 kcal/mol.

(2*R*,3a*R*,12b*S*,12c*R*)-2,3,3a,5,6,8,12b,12c-Octahydro-8-oxo-1*H*,4*H*-pyrido[3,2,1-*de*]phenanthridine-3a,2-carbolactone (17): mp 253–254 °C dec; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.06 (d, 1 H, J = 7.9 Hz), 7.48 (t, 1 H, J = 7.9 Hz), 7.39 (t, 1 H, J = 7.9 Hz), 7.13 (d, 1 H, J = 7.9 Hz), 5.06 (t, 1 H, J = 5.9 Hz), 4.43 (dm, 1 H, J = 13.0 Hz), 3.47 (d, 1 H, J = 12.0 Hz), 3.27 (ddd, 1 H, J = 7.6, 12.0, 12.5 Hz), 2.92 (dt, 1 H, J = 3.2, 13.0 Hz), 2.78 (d, 1 H, J = 12.4 Hz), 2.62 (ddd, 1 H, J = 7.6, 15.4), 2.16 (dt, 1 H, J = 3.1, 13.9 Hz), 2.12–2.07 (m, 1 H), 2.05–2.00 (m, 2 H), 1.76 (dm, 1 H, J = 13.9 Hz), 1.59 (tq, 1 H, J = 2.9, 12.7 Hz); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 179.4, 166.2, 140.0, 132.2, 128.8, 127.4, 122.4, 74.8, 55.9, 43.6, 41.3, 37.1, 34.5, 30.9, 28.9, 20.5 (one aromatic resonance could not be located); IR ($CHCl_3$) 1775, 1640 cm^{-1}; $[\alpha]^{24}_D$ = +56.7° (c 0.67, $CHCl_3$); CI-MS m/z (relative intensity) 284 (100); HRMS (M + H)$^+$ calcd for $C_{17}H_{17}NO_3$ 284.1287, found 284.1284. Diagnostic NOESY data (1:1 $CDCl_3$:C_6D_6, 500 MHz) for determination of stereochemistry at C(12c) and C(12b):

proton	NOE interaction	distance, Å (Macromodel)
12b (3.27 ppm)	12c (3.47 ppm)	3.1
	6ax (2.92 ppm)	4.1
	3ax (2.78 ppm)	2.2
12c (3.47 ppm)	3ax	3.8
	1eq (2.62 ppm)	3.0

(4a*R*,6*R*)-*N*-Benzoyl-1,2,3,4,4a,5,6,7-octahydro-quinoline-4a,6-carbolactone (18): ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38 (m, 2 H), 7.30 (m, 3 H), 4.75 (t, 1 H, J = 3.2 Hz), 4.69 (m, 1 H), 3.93 (m, 1 H), 3.59 (m, 1 H), 2.34 (dt, 1 H, J = 3.2, 13.2 Hz), 2.31 (dm, 1 H, J = 19.6 Hz), 2.20 (dd, 1 H, J = 4.6, 11.2 Hz), 2.11 (m, 1 H), 2.09 (d, 1 H, J = 11.2 Hz), 1.95 (dm, 1 H, 19.6 Hz), 1.75–1.60 (m, 2 H); IR ($CHCl_3$) 1775, 1635 cm^{-1}; CI-MS m/z (relative intensity) 284 (M^+ + 1, 100), 180 (5), 105 (10).

(4a*R*,5*R*,6*R*)-*N*-(2-Bromoacetyl)-5-iodo-1,2,3,4,4a,5,6,7-octahydroquinoline-4a,6-carbolactone (19). To a solution of **6** (88 mg, 0.289 mmol) in THF (6 mL) at 0 °C were added $NaHCO_3$ (31 mg, 0.376 mmol) and bromoacetyl chloride (26 μL, 0.317 mmol). The solution was warmed to room temperature and stirred overnight, and then 25 mL of H_2O was added. The mixture was extracted with three 25 mL portions of CH_2Cl_2, and the organic extracts were dried over Na_2SO_4, filtered, and evaporated. Column chromatography (silica gel, 1:2

EtOAc:hexane) gave 86.2 mg (70%) of **19** as a clear oil. Due to the instability of **19** upon storage, it was used in the next reaction shortly after chromatography: TLC R_f = 0.5 (1:1 EtOAc:hexane, I_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90 (s, br, 1 H), 4.76 (m, 1 H), 4.49 (d, 1 H, J = 5.1 Hz), 3.92 (s, 2 H), 3.89–3.97 (m, 1 H), 3.47 (m, 1 H), 3.10 (td, 1 H, J = 3.0, 19.7 Hz), 2.76 (td, 1 H, J = 2.9, 19.7 Hz), 2.11 (m, 2 H), 1.99 (m, 1 H), 1.84 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2, 166.7, 116.6, 75.8, 47.0, 43.7, 30.2, 25.7, 25.4, 23.8, 19.1 (one carbon resonance could not be located); IR (film) 1770, 1650 cm^{-1}; CI-MS *m/z* (relative intensity) 428 (M^+ + 1, 28), 426 (28), 382 (10), 348 (22), 346 (32), 302 (12), 300 (12), 222 (80), 220 (100); $[\alpha]^{24}_D$ +195.7° (*c* 0.87, CH_2Cl_2).

(6a*R*,8*R*,9a*R*,9b*S*)-1,4,5,6,7,9,9a,9b-Octahydro-2-oxopyrrolo[3,2,1-*ij*]quinoline-6a,8-carbolactone (20). A solution of **19** (55 mg, 0.129 mmol), Bu_3SnH (75 μL, 0.278 mmol), and AIBN (2.5 mg, 0.015 mmol) in benzene (14 mL, *c* 0.009 M) was degassed by bubbling N_2 through the solution for 15 min. The solution was refluxed under N_2 for 4 h, and then 1 mg of AIBN was added and the solution was refluxed overnight. The reaction mixture was cooled, concentrated, and chromatographed (silica gel, 1–2% MeOH in EtOAc) to give, in order of elution, 8.5 mg (30%) of **21** and 18.0 mg (63%) of **20**. **20**: mp 145–147 °C; TLC R_f = 0.11 (EtOAc, I_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.84 (m, 1 H), 4.23 (dd, 1 H, J = 5.6, 12.7 Hz), 3.48 (d, 1 H, J = 8.3 Hz), 2.70–2.90 (m, 3 H), 2.48 (d, 2 H, J = 10.7 Hz), 2.30 (ddd, 1 H, J = 1.7, 5.9, 12.0 Hz), 2.26 (dm, 1 H, J = 18.8 Hz), 1.95–2.01 (m, 2 H), 1.72 (d, 1 H, J = 11.8 Hz), 1.61 (dt, 1 H, J = 4.6, 13.4 Hz), 1.50–1.55 (m, 1 H); ^{1}H NMR (C_6D_6, 500 MHz) δ 4.44 (dd, 1 H, J = 5.9, 12.9 Hz), 4.01 (m, 1 H), 2.97 (m, 1 H), 2.56 (dd, 1 H, J = 11.9, 17.1 Hz), 2.50 (d, 1 H, J = 8.3 Hz), 2.43 (dt, 1 H, J = 3.4, 12.4 Hz), 2.23 (dd, 1 H, J = 10, 17.1 Hz), 1.99 (m, 1 H), 1.57 (dm, 1 H, J = 13.4 Hz), 1.51 (dm, 1 H, 14.9 Hz), 1.41 (ddd, 1 H, J = 1.9, 5.9, 11.7 Hz), 1.07–1.10 (m, 1 H), 0.97 (ddd, 1 H, J = 1.7, 8.8, 15.1 Hz), 0.93 (dt, 1 H, J = 4.7, 13.4 Hz), 0.67 (d, 1 H, J = 11.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.2, 171.9, 75.5, 64.1, 42.8, 39.6, 39.5, 37.1, 29.6, 29.3, 27.0, 19.7; IR (film) 1765, 1670 cm^{-1}; $[\alpha]^{22}_D$ = −70.0° (*c* 1.0, $CHCl_3$); CI-MS *m/z* (relative intensity) 222 (M^+ + 1, 100); HRMS (M^+ + 1) calcd for $C_{12}H_{15}NO_3$ 222.1130, found 222.1129. Diagnostic NOESY data (1:1 $CDCl_3$:C_6D_6, 500 MHz) for determination of stereochemistry at C(9b) and C(9a):

proton	NOE interaction	distance, Å (Macromodel)
9b (3.48 ppm)	7 (1.72 ppm)	2.48

All four possible diastereomers from radical cyclization were minimized and modeled using Macromodel. **20**, $J_{H9b-H9a}$ observed = 8.3 Hz. The calculated Macromodel data: $J_{H9b\alpha-H9a\alpha}$ = 7.8 Hz, 14.8 kcal/mol; $J_{H9b\alpha-H9a\beta}$ = 11.4 Hz, 19.7 kcal/mol; $J_{H9b\beta-H9a\beta}$ = 7.8 Hz, 12.7 kcal/mol; $J_{H9b\beta-H9a\alpha}$ = 11.2 Hz, 23.3 kcal/mol.

(4a*R*,6*R*)-*N*-Acetyl-1,2,3,4,4a,5,6,7-octahydroquinoline-4a,6-carbolactone (21): TLC R_f = 0.30 (EtOAc, I_2); mp 111–112 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.41 (s, 1 H), 4.85 (m, 1 H), 3.95 (m, 1 H), 3.31 (dd, 1 H, J = 6.1, 12.5), 2.63 (td, 1 H, J = 3.1, 19.3 Hz), 2.57 (td, 1 H, J = 3.0, 19.3 Hz), 1.96–21.0 (m, 3 H), 2.05 (s, 3 H), 1.94–2.02 (m, 1 H), 1.61–1.66 (m, 1 H), 1.52–1.60 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.9, 170.7, 137.6, 118.3, 73.4, 46.4, 44.5, 38.6, 31.8, 25.1, 21.5, 19.4; IR (film) 1765, 1645 cm^{-1}; CI-MS *m/z* (relative intensity) 222 (M^+ + 1, 100).

(7a*R*,10a*R*,10b*S*)-2,3,6,7,7a,8,9,10,10a,10b-Decahydro-5,9-dioxo-10a-carboxy-1*H*,5*H*-benzo[*ij*]quinolizine (22). A solution of **8** (50 mg, 0.213 mmol) in 1 mL of THF and 1 M KOH (425 μL, 0.426 mmol) was stirred overnight at room temperature. After evaporation of solvent, the residue was dissolved in 0.0185 M aqueous Na_2RuO_4[17a] (12.0 mL, 0.224 mmol); a black precipitate was apparent nearly immediately. After 2 h of stirring at room temperature, 0.5 mL of MeOH was added. The solution was filtered and the precipitate rinsed with small portions of 1 M KOH. The filtrate was acidified to pH 2 with 6 M HCl, saturated with sodium chloride, and extracted four times with 50 mL portions of $CHCl_3$. The organic layer was dried over Na_2SO_4, filtered, and evaporated to give 38 mg of a yellow solid. The residue was chromatographed (silica gel; 6% MeOH in CH_2Cl_2) to give 25 mg (46%) of **22** as a white solid: mp 265–266 °C dec; TLC R_f = 0.15 (10% MeOH in CH_2Cl_2, I_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.85 (s, br, 1 H), 4.84 (dm, 1 H, J = 12.2 Hz), 3.60 (d, 1 H, 7.0 Hz), 2.49–2.54 (m, 4 H), 2.47 (dd, 1 H, J = 1.2, 5.1 Hz), 2.20–2.32 (m, 2 H), 2.15 (dt, 1 H, J = 4.2, 13.2 Hz), 2.09 (d, 1 H, 15.1 Hz), 2.04 (dd, 1 H, J = 4.6, 13.2 Hz), 1.97 (d, 1 H, J = 13.6 Hz), 1.52–1.64 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.5, 169.9, 61.7, 48.3, 47.3, 43.9, 41.0, 33.0, 31.9, 31.5, 25.5, 21.4; IR (CH_2Cl_2) 3250 br, 1770, 1720, 1635, 1600 cm^{-1}; $[\alpha]^{24}_D$ = +8.0° (*c* 0.75, $CHCl_3$); CI-MS *m/z* (relative intensity) 252 (M^+ + 1, 100), 206 (25). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.02; H, 6.81; N, 5.48.

(7a*R*,10b*S*)-2,3,6,7,7a,8,9,10b-Octahydro-5,9-dioxo-10a-carboxy-1*H*,5*H*-benzo[*ij*]quinolizine (23). A solution of **22** (23 mg, 0.0916 mmol) in CH_3CN (1.8 mL) was degassed with N_2 for 5 min. $Pb(OAc)_4$ (50 mg, 0.114 mmol) was added, and the solution was stirred in the dark for 1 h to give an orange solution. The solution was irradiated (366 nm light source) to give a light yellow solution and a white precipitate. A mixture of H_2O and ethylene glycol (2:1, 0.5 mL) was added to destroy the excess $Pb(OAc)_4$. An additional 10 mL of H_2O was added, and then the solution was extracted with three 15 mL portions of CH_2Cl_2. The organic layer was washed once with 10 mL of saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated to give 16 mg of a yellow oil. Column chromatography (silica gel, 1–5% MeOH in CH_2Cl_2) gave 9.4 mg (50%) of **23** (oil). Crystallization occurred upon storage in the freezer: mp 106–108 °C dec.; TLC R_f = 0.52 (10% MeOH in CH_2Cl_2, UV, I_2); ^{1}H NMR (C_6D_6, 500 MHz) δ 5.56 (s, 1 H), 4.76 (dm, 1 H, J = 12.9 Hz), 3.14 (d, 1 H, J = 6.1 Hz), 2.15 (ddd, 1 H, J = 3.7, 4.9, 17.1 Hz), 1.99 (dt, 1 H, J = 4.2, 13.9 Hz), 1.92 (dd, 1 H, J = 5.1, 16.3 Hz), 1.87 (dm, 1 H, J = 17.1 Hz), 1.75 (dm, 1 H, J = 16.3), 1.52–1.63 (m, 2 H), 1.15–1.29 (m, 3 H), 1.04 (m, 1 H), 0.84–0.89 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.5, 168.7, 157.0, 124.4, 58.0, 43.2, 41.8, 32.8, 32.7, 31.4, 24.4, 23.6; IR (film) 1680, 1640 cm^{-1}; $[\alpha]^{27}_D$ = −112.3° (c = 1.3, CH_2Cl_2); CI-MS *m/z* (relative intensity) 206 (M^+ + 1, 100); HRMS (M^+ + 1) calcd for $C_{12}H_{15}NO_2$ 205.1103, found 205.1101. **24**: ^{1}H NMR ($CHCl_3$, 500 MHz) (from a crude 4:1 mixture of **23**:**24** before chromatography) δ 5.7 (m, 1 H), 4.73 (dd, 1 H, J = 6.1, 13.1 Hz), 3.00 (d, 1 H, J = 12.9 Hz), the remaining signals were overlapping with those of **23**.

Isomerization of 24 to 23. To an 8 mg crude sample of **23**:**24** (4:1 ratio, obtained from procedure described above) in 10 mL of CH_2Cl_2 was added silica gel to give a slurry. After stirring overnight under N_2, the silica gel was filtered and rinsed with 2% MeOH in CH_2Cl_2. The filtrate was evaporated, dissolved in CH_2Cl_2 and filtered again to give 4.5 mg of **23** as an oil (45% yield based on theory from **22**).

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Supporting Information Available: ^{1}H NMR spectra of **12**, **13**, **16**, **20**, and **23** and ^{13}C NMR spectrum of **17** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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