JOC Article

Total Synthesis of Mappicine Ketone (Nothapodytine B) by Means of Sulfur-Directed 5-*exo*-Selective Aryl Radical Cyclization onto Enamides

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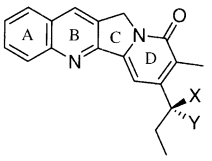
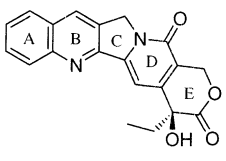
Enamides **5**, on treatment with Bu_3SnH−AIBN, underwent aryl radical cyclization in a 5-*exo* manner to give 1-[bis(phenylthio)methyl]dihydroisoindoles **6**, which were partially desulfurized with Bu_3SnH−AIBN to give 1-mono(phenylthio)methyl congeners **7**. Formation of **6** from **5** may be explained by the presence of two phenylthio groups at the terminus of the *N*-vinylic bond of **5**, since enamide **8a** having no phenylthio group underwent aryl radical cyclization in a 6-*endo* manner. Compound **7d** (R = CF_3) was transformed into sulfoxide **16**, which was treated with $(CF_3CO)_2O$ and then with 10% NaOH to give a model compound **20** of mappicine ketone (MPK) (**1**) through aldol condensation of aldehyde **18**. An attempt to synthesize MPK using this method with sulfoxide **28** prepared from **25**, however, was unsuccessful, and, instead, photochemical cyclization of enamide **38** prepared from **25** furnished MPK.

Introduction

Mappicine ketone (MPK) (**1**) has recently been identified as an antiviral lead compound with selective activities against herpesviruses HSV-1 and HSV-2 and human cytomegalovirus (HCMV).[1] MPK is an oxidized derivative of mappicine (**2**) and an E ring decarboxylated analogue of camptothecin (**3**)[2] that exhibits potent cytotoxic activity against a wide range of tumor cell lines. Camptothecin is now obtained easily in large quantity from natural sources, but MPK has not been isolated in sufficient amounts for further studies. Many efforts have therefore been made recently to improve the degradation[3] of camptothecin as well as to develop new methods for synthesizing MPK and related compounds.[4,5]



1: X, Y = O (Mappicine Ketone)
2: X = OH, Y = H (Mappicine)



3: Camptothecin

In a previous communication,[6] we reported that treatment of enamides **5** with Bu_3SnH−AIBN resulted in aryl radical cyclization in a 5-*exo* manner to give 1-(phenylthiomethyl)dihydroisoindoles **7** through partial desulfurization of the initial products **6** (Scheme 1). We also reported that intramolecular aldol condensation of aldehyde **18** derived from aryl radical cyclization product **7d** afforded a model compound **20** of MPK (Scheme 4). We attempted the synthesis of MPK using this method with **25**, but, unfortunately, the crucial aldol condensation of **29** gave an unexpected result (Scheme 5). We then devised an alternative method for the synthesis of MPK and found that photochemical cyclization of enamide **38** prepared from **25** furnished MPK via oxidation of the intermediate **39** (Scheme 7). In this paper, we describe these results

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(1) Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem.* **1994**, *59*, 2623. Pendrak, I.; Wittrock, R.; Kingsbury, W. D. *J. Org. Chem.* **1995**, *60*, 2912.

(2) For total and formal total syntheses of camptothecin or its derivatives, see: Tagami, K.; Nakazawa, N.; Sano, S.; Nagao, Y. *Heterocycles* **2000**, *53*, 771. Brown, R. T.; Jianli, L.; Santos, C. A. M. *Tetrahedron Lett.* **2000**, *41*, 859. Bennasar, M.-L.; Juan, C.; Bosch, J. *Chem. Commun.* **2000**, 2459. Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255. Gabarda, A. E.; Du, W.; Isarno, T.; Tangirala, R. S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 6329. Blagg, B. S. J.; Boger, D. L. *Tetrahedron* **2002**, *58*, 6343. Thomas, O. P.; Zaparucha, A.; Husson, H.-P. *Eur. J. Org. Chem.* **2002**, 157. Curran, D. P.; Du, W. *Org. Lett.* **2002**, *4*, 3215. See also references therein.

(3) For transformation of camptothecin to MPK, see: Kingsbury, W. D. *Tetrahedron Lett.* **1988**, *29*, 6847. Fortunak, J. M. D.; Mastrocola, A. R.; Mellinger, M.; Wood, J. L. *Tetrahedron Lett.* **1994**, *35*, 5763. Das, B.; Madhusudhan, P.; Kashinatham, A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1403. Das, B.; Madhusudhan, P. *Tetrahedron* **1999**, *55*, 7875.

(4) For total and formal total syntheses of mappicine or mappicine ketone (MPK), see: (a) Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **1998**, *120*, 1218. (b) Mekouar, K.; Génisson, Y.; Leue, S.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 5212. (c) Toyota, M.; Komori, C.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 7110. (d) Zhang, Q.; Rivkin, A.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 5774. (e) Carles, L.; Narkunan, K.; Penlou, S.; Rousset, L.; Bouchu, D.; Ciufolini, M. A. *J. Org. Chem.* **2002**, *67*, 4304. See also references therein.

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(6) Ishibashi, H.; Kato, I.; Takeda, Y.; Tamura, O. *Tetrahedron Lett.* **2001**, *42*, 931.

10.1021/jo030177m CCC: $25.00
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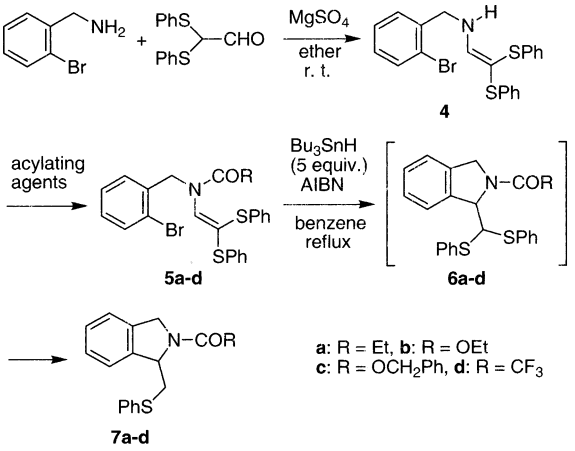
SCHEME 1



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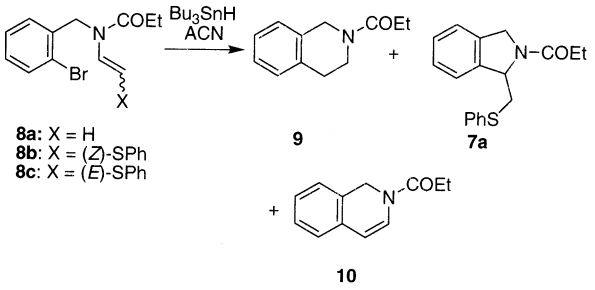

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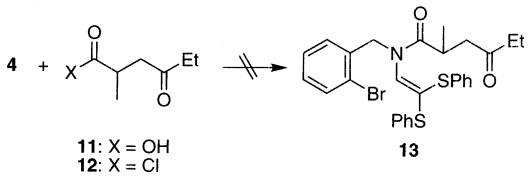


together with a full account of preliminary works in this area.

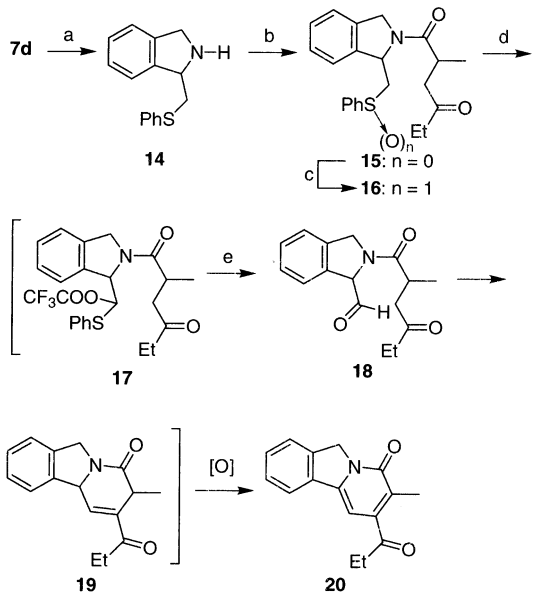
Results and Discussion

Condensation of *o*-bromobenzylamine with bis(phenylthio)acetaldehyde[7] gave enamine **4** in 69% yield. Compound **4** was then treated with propionyl chloride in the presence of diethylaniline in boiling benzene to give enamide **5a** in 78% yield. Similar treatment of **4** with alkoxycarbonyl chlorides gave **5b** and **5c** in 72 and 51% yields, respectively. On the other hand, treatment of **4** with $(CF_3CO)_2O$ in the presence of triethylamine gave trifluoroacetyl compound **5d** in 92% yield.

When enamide **5a** was treated with 1.1 equiv of Bu_3SnH in the presence of AIBN in boiling benzene, the 5-*exo* aryl radical cyclization product **6a** was obtained in 38% yield along with the partially desulfurized compound **7a** (27% yield). On the other hand, treatment of **5a** with 5 equiv of Bu_3SnH gave only **7a** in 68% yield. Similar treatment of **5b**, **5c**, and **5d** afforded **7b**, **7c**, and **7d** in 84, 68, and 85% yields, respectively.

A previous study in our laboratory revealed that enamide **8a** having no PhS group at the terminus of its *N*-vinylic bond underwent aryl radical cyclization in a 6-*endo* manner exclusively to give a tetrahydroisoquinoline derivative **9** (Scheme 2),[8] whereas enamide **8b** having a (*Z*)-PhS group afforded a 5-*exo* cyclization product **7a**. On the other hand, enamide **8c** having an (*E*)-PhS group showed an intermediate behavior to give **7a** and **10**.[9] The difference between the modes of cyclization of **8a**−**c** can be explained by the difference between the conformers of their enamide double bonds, and the exclusive formation of the 5-*exo* cyclization product **6** from **5** may therefore be ascribed to the presence of a (*Z*)-phenylthio group in **5** as in the case of **8b**.[10] Another reason for the preference for 5-*exo* closure of **5** to **6** may be that the presence of two PhS groups greatly stabilizes the resulting radical.

SCHEME 4[a]



[a] Reagents and conditions: (a) K_2CO_3, MeOH−H_2O (15:1), room temperature; (b) **11**, EDC, DMAP, HOBt, CH_2Cl_2, room temperature, 64% from **7d**; (c) MCPBA, CH_2Cl_2, 0 °C, 73%; (d) $(CF_3CO)_2O$, CH_2Cl_2, 0 °C; (e) 10% NaOH, MeOH, reflux, 45% from **16**.

The exclusive formation of **7** from **5** seems to be promising for the construction of B−C−D rings of MPK, since the sulfur atom incorporated into **7** would serve as a handle for elaboration of the D ring. For this purpose, enamide **13** would be the most suitable precursor for the synthesis of a model compound **20** via the radical cyclization product **15**. However, acylation of **4** with carboxyclic acid **11** or with the corresponding acid chloride **12** using conventional means was unsuccessful. Therefore, we decided to prepare compound **15** from **7b**, **7c**, or **7d**.

The alkaline hydrolysis of **7b**,**c** giving amine **14** required rather drastic conditions and a long reaction time. For example, heating **7b** with 40% aqueous KOH in boiling ethylene glycol for 3 h gave only a 51% yield of

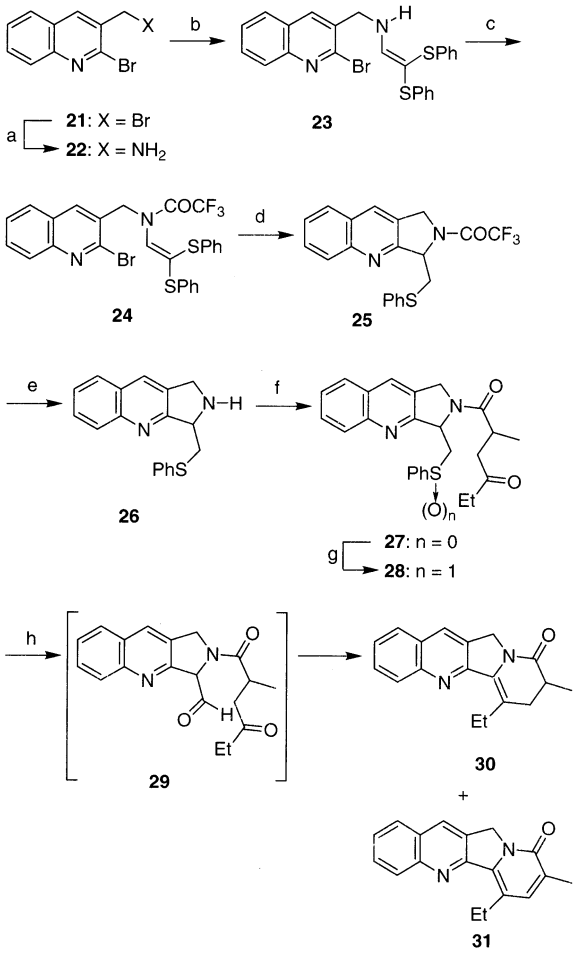
(7) Ishibashi, H.; Kameoka, C.; Iriyama, H.; Kodama, K.; Sato, T.; Ikeda, M. *J. Org. Chem.* **1995**, *60*, 1276.

(8) Ishibashi, H.; Kato, I.; Takeda, Y.; Kogure, M.; Tamura, O. *Chem. Commun.* **2000**, 1527.

(9) Formation of **10** might be a result of a consecutive 6-*endo* aryl radical cyclization of **8c** and an elimination of benzenethiyl radical from the resulting radical intermediate.

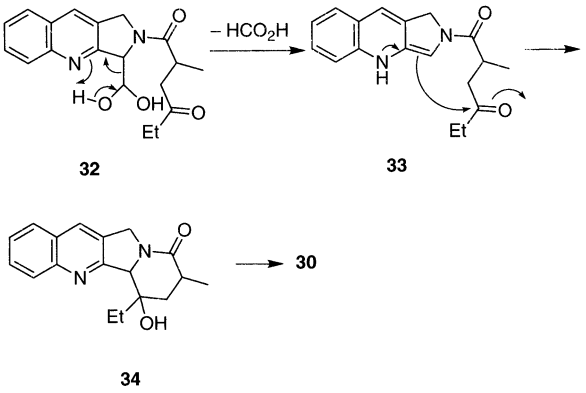
(10) For other sulfur-directed *exo*-selective radical cyclizations, see: Ishibashi, H.; Kawanami, H.; Nakagawa, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2291. Ishibashi, H.; Kobayashi, T.; Takamasu, D. *Synlett* **1999**, 1286. See also ref 7.

SCHEME 5[a]



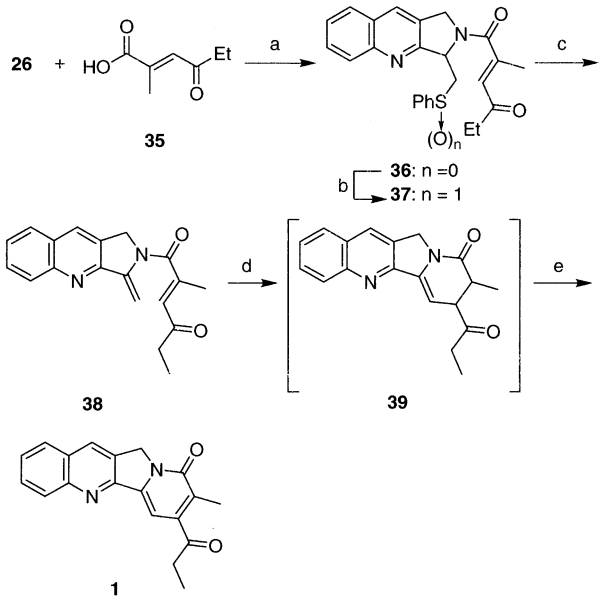
[a] Reagents and conditions: (a) aq NH_4OH, room temperature, 5 days, 91%. (b) $(PhS)_2CHCHO$, $MgSO_4$, Et_2O, room temperature, 10 h, 82%. (c) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, room temperature, 30 min, 84%. (d) Bu_3SnH, AIBN, benzene, reflux, 85%. (e) $NaBH_4$, EtOH, room temperature, 30 min. (f) **12**, Et_3N, CH_2Cl_2, room temperature, 13 h, 75% from **25**. (g) MCPBA, CH_2Cl_2, 0 °C, 72%. (h) (1) $(CF_3CO)_2O$, CH_2Cl_2, 0 °C; (2) 10% NaOH, MeOH, reflux, 62% from **28** for **30**, 5% from **28** for **31**.

SCHEME 6



14. On the other hand, hydrolysis of **7c** with 40% aqueous KOH in boiling MeOH required a 43 h period of heating to give **14** in 78% yield. Compound **7c** was therefore subjected to hydrogenolysis with a Willkinson's catalyst $[RhCl(PPh_3)_3]$ in benzene[11] or treated with trimethylsilyl iodide in acetonitrile, whereupon the starting material

SCHEME 7[a]



[a] Reagents and conditions: (a) EDC, CH_2Cl_2, room temperature 16 h, 75%; (b) MCPBA, CH_2Cl_2, 0 °C, 98%; (c) $CaCO_3$, toluene, reflux 13 h, 63%; (d) *hν*, MeOH, 1.5 h; (e) 10% Pd/C, CH_3CO_2H, 80 °C, 3 h, 28% from **38**.

was completely consumed, but no desired amine **14** could be obtained. The amine **14** was best prepared by treating trifluoroacetamide **7d** with K_2CO_3 in MeOH−H_2O (15:1) at room temperature. This amine was then acylated with carboxylic acid **11** in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), DMAP, and 1-hydroxybenzotriazole (HOBt) to give amide **15** in 64% yield (based on **7d**).

Oxidation of **15** with MCPBA (73%) followed by treatment of the resulting sulfoxide **16** with trifluoroacetic anhydride (TFAA) gave a Pummerer rearrangement product **17**. This compound, without purification, was then treated with 10% aqueous NaOH in boiling MeOH to give the target compound **20** in 45% yield (based on **16**). Formation of **20** from **17** can be explained by a three-step sequence of the reactions that involve alkaline hydrolysis of trifluoroacetate **17**, intramolecular aldol condensation of the resulting aldehyde **18**, and autoxidation of the six-membered unsaturated lactam **19**. It should be noted that no specific oxidizing agent such as DDQ was required in the final step. It is not clear at present whether compound **20** was formed from **19** or from its regioisomer with respect to the double bond.

Encouraged by the success of obtaining a model compound **20** for MPK, we next examined the cyclization of enamide **24** and the elaboration of the resulting product **25** to MPK (Scheme 5).

Synthesis of the requisite radical precursor **24** was begun by amination of 2-bromo-3-(bromomethyl)quinoline (**21**)[13] with NH_3 followed by condensation of the resulting amine **22**[4b] with bis(phenylthio)acetaldehyde to give enamine **23**. Acylation of **23** with $(CF_3CO)_2O$ gave **24** in 84% yield. Treatment of **24** with 5 equiv of Bu_3SnH and

(11) It has been reported that catalytic hydrogenation of sulfur-containing compounds such as allyl phenyl sulfide is effected with a Willkinson catalyst in benzene. See: Birch, A. J.; Walker, K. A. M. *Tetrahedron Lett.* **1967**, 1935.

AIBN gave the expected radical cyclzation product **25** in 85% yield. Deprotection of **25** with K_2CO_3 in aquoues MeOH required a longer reaction time than **7d**. Compound **25** was treated with $NaBH_4$ in EtOH for 30 min to give amine **26**. Acylation of **26** with acid chloride **12** gave amide **27** in 75% yield. Oxidation of **27** with MCPBA gave sulfoxide **28** (72%), which was treated with $(CF_3CO)_2O$ and then with 10% NaOH to give tetracyclic compound **30** in 62% yield along with a trace amount (5% yield) of its oxidized compound **31**. Unfortunately, no expected MPK was obtained from **29**.

The spectral data of compound **30** indicated it to be a product in which CO was eliminated from MPK. Formation of **30** may be explained as follows. Alkaline hydrolysis of the Pummerer rearrangement product derived from sulfoxide **28** gives aldehyde **29**, whose hydrate **32** eliminates HCO_2H with the aid of a nitrogen atom of the quinoline ring as shown in Scheme 6. Then the resulting enamine **33** attacks the internal carbonyl group to give **34**, whose elimination of water gives **30**.

On the basis of these results, we envisioned that the photochemical cyclization of enamide **38** would provide the D ring of MPK. Compound **38** was prepared by thermal elimination of benzenesulfenic acid of sulfoxide **37**, which, in turn, was prepared from amine **26** by acylation with unsaturated carboxylic acid **35** followed by oxidation of the resulting amide **36** with MCPBA. The thermal elimination of benzenesulfenic acid of sulfoxide **37** in boiling toluene in the presence of $NaHCO_3$ gave an unsatisfactory result, but the use of $CaCO_3$ in place of $NaHCO_3$ gave **38** in 63% yield. Compound **38** was irradiated with a low-pressure Hg lamp in a quartz tube, and then the reaction mixture containing **39** was treated with 10% Pd/C in acetic acid[12] to give MPK (**1**) in 28% yield with recovery of the starting material **38** (38%). The melting point (235−237 °C) and spectral data of MPK herein obtained were identical with the reported values (mp 236−237 °C).[4a] Other attempts to synthesize MPK (**1**) from **39** by treating with oxygen gas in MeOH, MnO_2 in benzene, DDQ in benzene, and $FeCl_3$ in MeOH failed.

Experimental Section

***N*-(*o*-Bromobenzyl)-*N*-[2,2-bis(phenylthio)ethenyl]propanamide (5a).** To a solution of *o*-bromobenzylamine (1.29 g, 6.91 mmol) in Et_2O (10 mL) were added bis(phenylthio)-acetaldehyde[7] (1.50 g, 5.76 mmol) and $MgSO_4$ (2 g), and the mixture was stirred at room temperature for 15 h. $MgSO_4$ was removed by filtration; the filtrate was concentrated, and the residue was chromatographed on silica gel (hexane/AcOEt, 16:1) to give enamine **4** (2.39 g, 97%) as an oil: ^{1}H NMR δ 4.41 (d, J = 6.3 Hz, 2H), 5.48−5.62 (m, 1H), 7.07−7.32 (m, 14H), 7.56 (d, J = 7.9 Hz, 1H). This enamine was used immediately in the next step. Propionyl chloride (260 mg, 2.81 mmol) was added to a boiling solution of enamine **4** (300 mg, 0.70 mmol) and *N*,*N*-diethylaniline (524 mg, 3.51 mmol) in benzene (15 mL), and the mixture was further heated under reflux for 2.5 h. After the mixture was cooled, water (15 mL) was added and the organic phase was separated. The aqueous phase was further extracted with AcOEt, and the combined organic phase was washed successively with a saturated aqueous $NaHCO_3$ solution, a saturated aqueous NH_4Cl solution, and brine and dried ($MgSO_4$). The solvent was evaporated off, and the residue was chromatographed on silica gel (hexane/AcOEt, 6:1) to give **5a** (265 mg, 78%) as an oil: IR ν 1665 cm^{-1}; ^{1}H NMR δ 1.17 (t, J = 7.3 Hz, 3H), 2.40 (q, J = 7.3 Hz, 2H), 5.01 (s, 2H), 7.04−7.28 (m, 14H), 7.54 (d, J = 7.9 Hz, 1H). Anal. Calcd for $C_{24}H_{22}BrNOS_2$: C, 59.50; H, 4.58; N, 2.89. Found: C, 59.66; H, 4.58; N, 2.91.

Ethyl *N*-(*o*-Bromobenzyl)-*N*-[2,2-bis(phenylthio)ethenyl]carbamate (5b). Using a procedure similar to that described above for **5a**, enamine **4** (224 mg, 0.52 mmol) was treated with ethoxycarbonyl chloride (170 mg, 1.56 mmol) in the presence of *N*,*N*-diethylaniline (312 mg, 2.10 mmol) in boiling benzene (10 mL) for 20 h. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 50:1 to 30:1) to give **5b** (187 mg, 72%) as an oil: IR ν 1710 cm^{-1}; ^{1}H NMR δ 1.30 (t, J = 7.0 Hz, 3H), 4.23 (q, J = 7.0 Hz, 2H), 5.06 (s, 2H), 6.90−7.40 (m, 14H), 7.49 (d, J = 7.9 Hz, 1H). Anal. Calcd for $C_{24}H_{22}BrNO_2S_2$: C, 57.60; H, 4.43; N, 2.80. Found: C, 57.32; H, 4.41; N, 3.00.

Benzyl *N*-(*o*-Bromobenzyl)-*N*-[2,2-bis(phenylthio)ethenyl]carbamate (5c). Using a procedure similar to that described above for **5a**, enamine **4** (208 mg, 0.49 mmol) was treated with benzyloxycarbonyl chloride (248 mg, 1.46 mmol) in the presence of *N*,*N*-diethylaniline (290 mg, 1.94 mmol) in boiling benzene (10 mL) for 20 h. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 50:1 to 30:1) to give **5c** (187 mg, 72%) as an oil: IR ν 1710 cm^{-1}; ^{1}H NMR δ 5.08 (s, 2H), 5.24 (s, 2H), 6.95−7.35 (m, 19H), 7.51 (d, J = 7.9 Hz, 1H). Anal. Calcd for $C_{29}H_{24}BrNO_2S_2$: C, 61.92; H, 4.30; N, 2.49. Found: C, 61.80; H, 4.41; N, 2.46.

***N*-(*o*-Bromobenzyl)-*N*-[2,2-bis(phenylthio)ethenyl]trifluoroacetamide (5d).** To a solution of enamine **4** (946 mg, 2.21 mmol) and Et_3N (671 mg, 6.63 mmol) in toluene (10 mL) was added $(CF_3CO)_2O$ (928 mg, 4.42 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 10:1) to give **5d** (1.06 g, 92%) as an oil: IR ν 1705 cm^{-1}; ^{1}H NMR δ 5.06 (s, 2H), 6.48 (s, 1H), 7.03−7.34 (m, 13H), 7.59 (d, J = 7.6 Hz, 1H). Anal. Calcd for $C_{23}H_{17}BrF_3NOS_2$: C, 52.68; H, 3.27; N, 2.67. Found: C, 52.44; H, 3.26; N, 2.53.

Radical Cyclization of 5a with 1.1 Equiv of Bu_3SnH. General Procedure. To a boiling solution of **5a** (212 mg, 0.45 mmol) in benzene (60 mL) was added dropwise a solution of Bu_3SnH (144 mg, 0.495 mmol) and AIBN (14.8 mg, 0.09 mmol) in benzene (60 mL) via syringe over a period of 3 h, and the mixture was further heated under reflux for 4 h. After evaporation of the solvent, Et_2O (50 mL) and 8% aqueous KF (20 mL) were added to the residue, and the whole was vigorously stirred at room temperature for 1 h. The organic phase was separated and the aqueous layer was further extracted with Et_2O. The combined organic phase was dried ($MgSO_4$) and concentrated, and the residue was chromatographed on silica gel (hexane/AcOEt, 3:1). The first fraction gave 1-bis(phenylthio)methyl-2-propionyldihydroisoindole (**6a**) (69 mg, 38%): mp 122−124 °C (hexane); IR ν 1640 cm^{-1}; ^{1}H NMR δ 1.12 (t, J = 7.3 Hz, 3H), 2.02−2.36 (m, 2H), 4.68 (d, J = 13.5 Hz, 1H), 4.83 (d, J = 13.5 Hz, 1H), 5.78 (s, 2H), 7.10−7.40 (m, 12H), 7.66 (d, J = 7.3 Hz, 1H), 7.88 (d, J = 6.6 Hz, 1H). Anal. Calcd for $C_{24}H_{23}NOS_2$: C, 71.08; H, 5.72; N, 3.45. Found: C, 71.04; H, 5.75; N, 3.37. The second fraction gave 1-phenylthiomethyl-2-propionyldihydroisoindole (**7a**) (36 mg, 27%) as an oil: IR ν 1645 cm^{-1}; ^{1}H NMR δ 1.08 (t, J = 7.3 Hz, 3H), 1.99 (dq, J = 16.2, 7.6 Hz, 1H), 2.22 (dq, J = 16.2, 7.6 Hz, 1H), 3.50 (dd, J = 13.9, 2.5 Hz, 1H), 3.85 (dd, J = 13.9, 5.6 Hz, 1H), 4.67 (s, 2 H), 5.59 (dd, J = 5.6, 2.5 Hz, 1H), 7.08−7.36 (m, 9H); ^{13}C NMR δ 9.0, 28.1, 38.0, 53.3, 62.6, 122.7, 123.7, 126.2, 128.1, 128.5, 129.1, 129.4, 136.8, 137.2, 139.4, 173.1; HRMS calcd for $C_{18}H_{19}NOS$ (M^+) 297.1187, found 297.1183.

Radical Cyclization of 5a with 5 Equiv of Bu_3SnH. Following the general procedure, a solution of **5a** (120 mg, 0.25 mmol) in boiling benzene (30 mL) was treated with a solution

(12) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955. For a similar reaction, see: ref 4b.

(13) Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc.* **1992**, *114*, 10971.

of Bu_3SnH (361 mg, 1.24 mmol) and AIBN (20 mg, 0.12 mmol) in benzene (50 mL). After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 2:1) to give **7a** (51 mg, 69%).

Radical Cyclization of 5b. Following the general procedure, a solution of **5b** (193 mg, 0.39 mmol) in boiling benzene (40 mL) was treated with a solution of Bu_3SnH (560 mg, 1.93 mmol) and AIBN (32 mg, 0.19 mmol) in benzene (40 mL). After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 8:1) to give 2-ethoxycarbonyl-1-(phenylthiomethyl)dihydroisoindole (**7b**) (101 mg, 84%) as an oil: IR ν 1690 cm^{-1}; ^1H NMR δ 1.23−1.32 (m, 3H), 3.33 (dd, J = 13.5, 7.3 Hz, 3/7H), 3.52−3.72 (m, 1H + 4/7H), 4.01−4.20 (m, 2H), 4.57−4.83 (m, 2H), 5.25 (m, 3/7H), 5.38 (m, 4/7H), 7.09−7.43 (m, 9H). Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11 N, 4.47. Found: C, 68.93; H, 6.22; N, 4.22.

Radical Cyclization of 5c. Following the general procedure, a solution of **5c** (329 mg, 0.59 mmol) in boiling benzene (60 mL) was treated with a solution of Bu_3SnH (853 mg, 2.93 mmol) and AIBN (48 mg, 0.29 mmol) in benzene (60 mL). After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 10:1) to give 2-benzyloxycarbonyl-1-(phenylthiomethyl)dihydroisoindole (**7c**) (375 mg, 68%) as an oil: IR ν 1700 cm^{-1}; ^1H NMR δ 3.30 (dd, J = 13.7, 7.1 Hz, 1/3H), 3.52 (dd, J = 13.5, 2.6 Hz, 1/3H), 3.56 (dd, J = 13.7, 2.8 Hz, 2/3H), 3.68 (dd, J = 13.9, 5.9 Hz, 2/3H), 4.64 (d, J = 14.5 Hz, 1/3H), 4.69 (d, J = 14.8 Hz, 1/3H), 4.73 (d, J = 14.5 Hz, 2/3H), 4.82 (d, J = 14.8 Hz, 2/3H), 5.00 (d, J = 12.5 Hz, 2/3H), 5.13 (s, 2/3H), 5.15 (d, J = 12.2 Hz, 2/3H), 5.24 (br d, J = 6.9 Hz, 1/3H), 5.38 (m, 2/3H), 7.09−7.32 (m, 14H). Anal. Calcd for $C_{23}H_{21}NO_2S$: C, 73.57; H, 5.64; N, 3.73. Found: C, 73.49; H, 5.71; N, 3.71.

Radical Cyclization of 5d. Following the general procedure, a solution of **5d** (289 mg, 0.553 mmol) in boilng benzene (60 mL) was treated with a solution of Bu_3SnH (804 mg, 2.76 mmol) and AIBN (45 mg, 0.286 mmol) in benzene (60 mL). After workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 15:1) to give 1-phenylthiomethyl-2-(trifluoroacetyl)dihydroisoindole (**7d**) (159 mg, 85%) as an oil: IR ν 1690 cm^{-1}; ^1H NMR δ 3.55 (dd, J = 14.2, 2.6 Hz, 1H), 3.73 (dd, J = 14.2, 5.9 Hz, 1H), 4.92 (d, J = 13.9 Hz, 1H), 4.98 (d, J = 13.9 Hz, 1H), 5.65 (dd, J = 5.9, 2.6 Hz, 1H), 7.12−7.37 (m, 9H). Anal. Calcd for $C_{17}H_{14}F_3NOS$: C, 60.53; H, 4.18; N, 4.15. Found: C, 60.60; H, 4.24; N, 4.15.

2-Methyl-4-oxohexanoic Acid (11). A mixture of methyl 3-oxopentanoate (6.51 g, 50 mmol), methyl 2-bromopropionate (7.55 g, 50 mmol), K_2CO_3 (35.0 g), and tetrabutylammonium iodide (3.70 g, 10 mmol) in acetone (200 mL) was stirred vigorously at room temperature for 3 h. Inorganic materials were filtered off; the solvent was evaporated off, and AcOEt was added to the residue. The organic phase was washed successively with water and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 8:1) to give alkylation product (9.90 g, 92%). This compound was dissolved in a mixed solvent of AcOH (100 mL), concentrated HCl (50 mL), and water (25 mL), and the mixture was heated under reflux for 4 h. AcOH was removed by evaporation; water was added to the residue, and the whole was extracted with Et_2O. The organic phase was dried ($MgSO_4$), and the solvent was evaporated off to give carboxylic acid **11** (5.87 g, 89%) as an oil: IR ν 1715 cm^{-1}; ^1H NMR δ 1.06 (t, J = 7.3 Hz, 3H), 1.22 (d, J = 6.9 Hz, 3H), 2.41−2.52 (m, 3H), 2.84−3.06 (m, 2H), 9.8−10.6 (br, 1H). Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.17; H, 8.41.

2-Methyl-4-oxohexanoyl Chloride (12). To a solution of carboxylic acid **11** (1.0 g, 6.94 mmol) and pyridine (1.1 g, 13.9 mmol) in benzene (1 mL) was added oxalyl chloride (2.63 g, 20. 8 mmol), and the mixture was stirred at room temperature for 1 h. After the solvent was evaporated off, Et_2O was added to the residue, and the precipitated salts were removed by filtration. The solvent was evaporated off to give acid chloride **12** (1.12 g, quant.).

2-(2-Methyl-4-oxohexanoyl)-1-(phenylthiomethyl)dihydroisoinole (15). A mixture of **7d** (50.0 mg, 1.15 mmol) and K_2CO_3 (50 mg) in MeOH/H_2O (15:1) (1.6 mL) was stirred at room temperature for 6 h. After removal of MeOH, water was added to the residue and the whole was extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The residue containing 1-(phenylthiomethyl)-dihydroisoindole (**14**) was dissolved in CH_2Cl_2 (2 mL), and to this solution were added carboxylic acid **11** (43 mg, 0.297 mmol), EDC (57 mg, 0.287 mmol), and HOBt (40 mg, 0.297 mmol). The mixture was stirred at room temperature for 1.5 h; water was added to the reaction mixture, and the whole was extracted with AcOEt. The organic phase was washed successively with 1 N HCl, 1 N NaOH, and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 5:1) to give **15** (35 mg, 64%) as an oil: IR ν 1710, 1640 cm^{-1}; ^1H NMR δ 0.89−1.40 (m, 6H), 2.42−2.52 (m, 3H), 2.84−3.13 (m, 2H), 3.32−3.72 (m, 2H), 4.80−5.18 (m, 2H), 5.49 (br d, J = 6.9 Hz, 2/3 H), 5.59 (m, 1/3H), 7.10−7.43 (m, 9H); ^{13}C NMR δ 8.0 (8.1), 17.3 (17.5), 33.6 (33.8), 36.3 (36.5), 37.4 (38.6), 46.4 (46.7), 53.0 (53.5), 62.2 (62.6), 122.7 (127.9), 123.6 (128.0), 124.2 (128.5), 125.9 (129.1), 129.2 (129.5), 136.9 (136.9), 139.1 (139.8), 175.9 (175.5), 210.4 (210.9) (the values in parentheses are probably due to the diasteroisomer); HRMS calcd for $C_{22}H_{25}NO_2S$ (M^+) 367.1606, found 367.1602.

2-(2-Methyl-4-oxohexanoyl)-1-(phenylsulfinylmethyl)-dihydroisoindole (16). To a solution of **15** (17 mg, 0.046 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of MCPBA (9.6 mg, 0.056 mmol) in CH_2Cl_2 (5 mL) at 0 °C over a period of 30 min. An aqueous $Na_2S_2O_3$ solution (5 mL) was added to the reaction mixture, and the whole was extracted with $CHCl_3$. The extract was washed successively with a saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 1:5) to give **16** (13 mg, 73%): ^1H NMR δ 0.99−1.29 (m, 6H), 2.42−2.58 (m, 3H), 3.06−3.19 (m, 2H), 3.34−3.74 (m, 2H), 4.86−5.30 (m, 2H), 5.61 (brd, 1/2H), 5.79 (brd, 1/2H), 7.28−7.70 (m, 9H). This compound was used immediately in the next step.

4,6-Dihydro-3-methyl-2-propanoylisoindolo[1,2-*a*]pyridin-4-one (20). To a solution of sufloxide **16** (10 mg, 0.026 mmol) in CH_2Cl_2 (5 mL) was added $(CF_3CO)_2O$ (78 mg, 0.37 mmol) at 0 °C, and the mixture was stirred at the same temperature for 3 h. The reaction mixture was concentrated; MeOH (2 mL) and 10% NaOH (0.2 mL) were added to the residue, and the mixture was heated under reflux for 30 min. Water was added to the reaction mixture, and the whole was extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 1:1 to 1:2) to give **20** (3 mg, 45%): IR ν 1705, 1655 cm^{-1}; ^1H NMR δ 1.23 (t, J = 7.3 Hz, 3H), 2.23 (s, 3H), 2.85 (q, J = 7.3 Hz, 2H), 5.14 (s, 2H), 6.64 (s, 1H), 7.45−7.78 (m, 4H); HRMS calcd for $C_{16}H_{15}NO_2$ (M^+) 253.1103, found 253.1106.

(2-Bromoquinolin-3-yl)methylamine (22). A solution of 2-bromo-3-(bromomethyl)quinoline (**21**)[13] (500 mg, 1.67 mmol) in 28% aqueous NH_4OH (150 mL) was stirred at room temperature for 5 days. The reaction mixture was extracted with $CHCl_3$, and the extract was washed with brine, dried (NaOH), and concentrated to give amine **22**[4b] (360 mg, 91%): mp 134−136 °C (Et_2O) (mp was not indicated in ref 4a); ^1H NMR δ 1.64 (s, 2H), 4.08 (s, 2H), 7.57 (t, J = 6.9 Hz, 1H), 7.71 (t, J = 6.9 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 8.04 (d, J = 8.3 Hz, 1H), 8.15 (s, 1H); ^{13}C NMR δ 46.3, 127.7, 127.9, 128.1, 128.7, 130.4, 136.1, 136.7, 144.0, 147.8.

***N*-(2-Bromoquinolin-3-yl)methyl-*N*-[2,2-bis(phenylthio)ethenyl]amine (23).** A mixture of amine **22** (342 mg, 1.45 mmol), bis(phenylthio)acetaldehyde[7] (415 mg, 1.59 mmol), and $MgSO_4$ (2 g) in Et_2O (10 mL) was stirred at room temperature for 10 h. $MgSO_4$ was removed by filtration; the filtrate was concentrated, and the residue was chromato-

graphed on silica gel (hexane/AcOEt, 16:1 to 6:1) to give enamine **23** (565 mg, 82%) as an oil: ^{1}H NMR δ 4.56 (d, J = 5.9 Hz, 2H), 5.55−5.70 (m, 1H), 7.10−7.39 (m, 11H), 7.55−7.65 (m, 1H), 7.70−7.78 (m, 2H), 7.90 (s, 1H), 8.06 (d, J = 9.3 Hz, 1H). This compound was used immediately in the next step.

***N*-(2-Bromoquinolin-3-yl)methyl-*N*-[2,2-bis(phenylthio)ethenyl]trifluoroacetamide (24).** To a solution of enamine **23** (296 mg, 0.62 mmol) and Et_3N (188 mg, 1.86 mmol) in CH_2Cl_2 (10 mL) was added $(CF_3CO)_2O$ (260 mg, 1.24 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. After workup as described above for **5a**, the crude material was chromatographed on silica gel (hexane/AcOEt, 8:1) to give **24** (299 mg, 84%) as an oil: IR ν 1700 cm^{-1}; ^{1}H NMR δ 5.17 (s, 2H), 6.56 (s, 1H), 7.03−7.23 (m, 10H), 7.61 (t, J = 6.9 Hz, 1H), 7.72−7.83 (m, 2H), 8.06 (d, J = 8.6 Hz, 1H), 8.11 (s, 1H); ^{13}C NMR δ 52.2, 118.7, 125.2, 125.4, 127.1, 127.1, 127.5, 128.0, 128.1, 128.2, 128.8, 129.0, 129.2, 129.3, 129.5, 131.0, 131.0, 133.0, 133.9, 136.4, 139.3, 148.4; HRMS calcd for $C_{26}H_{18}{}^{79}BrF_3N_2OS_2$ (M^+) 573.9996, found 573.9991.

7-Trifluoroacetyl-6,8-dihydro-6-(phenylthiomethyl)-pyrrolo[3,4-*b*]quinoline (25). Following the general procedure, a solution of **24** (130 mg, 0.226 mmol) in boiling benzene (50 mL) was treated with a solution of Bu_3SnH (330 mg, 1.13 mmol) and AIBN (19 mg, 0.113 mmol) in benzene (30 mL). After the usual workup, the crude material was chromatographed on silica gel (hexane/AcOEt, 6:1) to give **25** (159 mg, 85%): mp 134−136 °C (hexane); IR ν 1695 cm^{-1}; ^{1}H NMR δ 3.82 (dd, J = 14.5, 2.3 Hz, 1H), 4.25 (dd, J = 14.5, 4.1 Hz, 1H), 5.06 (d, J = 14.9 Hz, 1H), 5.15 (d, J = 14.9 Hz, 1H), 5.77 (dd, J = 4.1, 2.3 Hz, 1H), 6.85−7.13 (m, 5H), 7.56 (t, J = 6.9 Hz, 1H), 7.71 (t, J = 6.9 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.98 (s, 1H), 7.99 (d, J = 9.2 Hz, 1H); ^{13}C NMR δ 36.9, 51.8, 65.4, 126.8, 127.4, 128.2, 128.9, 129.6, 130.0, 130.1, 130.3, 135.3, 148.9, 158.8. Anal. Calcd for $C_{20}H_{15}F_3N_2OS$: C, 61.85; H, 3.89; N, 7.21. Found: C, 62.00; H, 3.92; N, 7.21.

7-(2-Methyl-4-oxohexanoyl)-6,8-dihydro-6-(phenylthiomethyl)pyrrolo[3,4-*b*]quinoline (27). To a solution of **25** (285 mg, 0.735 mmol) in EtOH (50 mL) was added $NaBH_4$ (55.6 mg, 1.47 mml) by portions, and the mixture was stirred at room temperature for 30 min. EtOH was evaporated off; water was added to the residue, and the whole was extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The residue containing amine **26** was dissolved in CH_2Cl_2 (2 mL), and to the solution were added Et_3N (372 mg, 3.68 mmol) and acid chloride **12** (357 mg, 2.21 mmol). The mixture was stirred at room temperature for 13 h; water was added to the reaction mixture, and the whole was extracted with $CHCl_3$. The extract was washed successively with a saturated aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give **27** (230 mg, 75%): IR ν 1710, 1645 cm^{-1}; ^{1}H NMR δ 0.98−1.25 (m, 3H), 2.34−2.53 (m, 2H + 4/5H), 2.75 (dd, J = 17.8, 6.6 Hz, 1/5H), 3.12−3.25 (m, 2H), 3.71 (dd, J = 13.9, 4.6 Hz, 1/5H), 3.81 (dd, J = 13.9, 2.0 Hz, 2/5H), 3.86 (dd, J = 13.9, 2.0 Hz, 2/5H), 4.01−4.05 (m, 1/5H), 4.17 (dd, J = 13.9, 8.9 Hz, 2/5H), 4.19 (dd, J = 13.9, 7.9 Hz, 2/5H), 4.84 (d, J = 16.8 Hz, 1/5H), 5.03 (br d, J = 14.2 Hz, 4/5H), 5.19 (d, J = 16.8 Hz, 1/5H), 5.22 (d, J = 14.2 Hz, 2/5H), 5.38 (d, J = 14.5 Hz, 2/5H), 5.69 (m, 4/5H), 6.02 (m, 1/5H), 6.80−6.93 (m, 3H), 7.02−7.07 (m, 2H), 7.51 (br t, J = 7.4 Hz, 1H), 7.66 (br t, J = 7.8 Hz, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.94 (br s, 2H); HRMS calcd for $C_{25}H_{26}N_2O_2S$ (M^+) 418.1715, found 418.1697.

7-(2-Methyl-4-oxohexanoyl)-6,8-dihydro-6-(phenylsulfinylmethyl)pyrrolo[3,4-*b*]quinoline (28). A solution of **27** (16 mg, 0.038 mmol) in CH_2Cl_2 (2 mL) was added dropwise a solution of MCPBA (80%) (9 mg, 0.041 mmol) in CH_2Cl_2 (2 mL) at 0 °C over a period of 30 min. An aqueous $Na_2S_2O_3$ solution was added to the reaction mixture, and the whole was extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$), and concenrated. The residue was chromatographed on silica gel (AcOEt) to give **28** (12 mg, 72%): ^{1}H NMR δ 0.93−1.14 (m, 3H), 1.19−1.37 (m, 3H), 2.35−2.64 (m, 3H), 3.12−3.36 (m, 2H), 3.46−3.74 (m, 1H), 3.83−4.07 (m, 1H), 5.06−5.54 (m, 2H), 5.70−5.80 (m, 1H), 7.35−7.47 (m, 3H), 7.51−7.61 (m, 3H), 7.67−7.88 (m, 2H), 7.98−8.12 (m, 2H). This compound was used immediately in the next step.

6-Ethyl-7,8-dihydro-8-methyl-11*H*-indolidino[1,2-*b*]quinolin-9-one (30) and 6-Ethyl-8-methyl-11*H*-indolidino[1,2-*b*]quinolin-9-one (31). To a solution of **28** (27 mg, 0.062 mmol) in CH_2Cl_2 (5 mL) was added $(CF_3CO)_2O$ (130 mg, 0.62 mmol) at 0 °C, and the mixture was stirred at the same temperature for 2 h. A saturated aqueous $NaHCO_3$ solution (1 mL), 10% NaOH (0.5 mL), and MeOH (5 mL) were added to the mixture, and the reaction mixture was heated under reflux for 15 min. Water was added to the reaction mixture, and the whole was extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 4:1 to 1:1). The first fraction gave **30** (11 mg, 62%): IR ν 1650 cm^{-1}; ^{1}H NMR δ 1.20 (t, J = 7.6 Hz, 3 H), 1.31 (d, J = 6.8 Hz, 3H), 2.37 (dd, J = 19.0, 12.2 Hz, 1H), 2.6−2.9 (m, 2H), 3.11 (dq, J = 15.1, 7.3 Hz, 1H), 3.28 (dq, J = 14.7, 7.3 Hz, 1H), 4.92 (d, J = 17.6 Hz, 1H), 4.97 (d, J = 17.6 Hz, 1H), 7.51 (ddd, J = 7.8, 6.8, 1.0 Hz, 1H), 7.68 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H), 7.77 (br d, J = 8.3 Hz, 1H), 8.02 (s, 1H), 8.08 (d, J = 8.8 Hz, 1H); HRMS calcd for $C_{18}H_{18}N_2O$ (M^+) 278.1419, found 278.1416. The second fraction gave **31** (0.8 mg, 5%): IR ν 1720, 1580 cm^{-1}; ^{1}H NMR δ 1.34 (t, J = 7.6 Hz, 3H), 2.31 (s, 3H), 3.41 (q, J = 7.5 Hz, 2H), 5.24 (s, 2H), 7.42 (s, 1H), 7.60 (br d, J = 8.0 Hz, 1H), 7.76 (br t, J = 8.0 Hz, 1H), 7.88 (br d, J = 8.3 Hz, 1H), 8.19 (d, J = 8.8 Hz, 1H), 8.28 (s, 1H); HRMS calcd for $C_{18}H_{16}N_2O$ (M^+) 276.1263, found 276.1263.

2-Methyl-4-oxohex-2-enoic Acid (35). LiOH (1.94 g, 46.2 mmol) was added to a solution of methyl (*E*)-2-methyl-4-oxo-2-hexenate (3.6 g, 23.1 mmol) in MeOH/H_2O (2:1, 60 mL), and the mixture was stirred at 0 °C for 2 h. The reaction mixture was acidified with 10% HCl to pH 1−2, and the whole was extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel ($CHCl_3$/MeOH, 30:1) to give **35** (3.07 g, 94%) as an oil: ^{1}H NMR δ 1.13 (t, J = 7.3 Hz, 3H), 2.22 (d, J = 1.7 Hz, 3H), 2.62 (q, J = 7.3 Hz, 2H), 7.20 (q, J = 1.3 Hz, 1H), 10.00−12.00 (br, 1H); ^{13}C NMR δ 8.1, 14.4, 38.5, 134.3, 139.7, 173.5, 202.8. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 58.81; H, 7.16.

7-(2-Methyl-4-oxohex-2-enoyl)-6,8-dihydro-6-(phenylthiolmethyl)pyrrolo[3,4-*b*]quinoline (36). According to a procedure similar to that dscribed above for **27**, amine **26** was obtained from compound **25** (514.6 mg, 1.33 mmol) by reduction with $NaBH_4$ (100.2 mg, 2.65 mmol) in EtOH (100 mL). A solution containing the crude amine **26**, EDC (506.7 mg, 2.65 mmol), and **35** in CH_2Cl_2 (15 mL) was stirred at room temperature for 16 h. Water was added, and the whole was extracted with $CHCl_3$. The organic phase was washed successively with a saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 3:2) to give **36** (415.1 mg, 75%): mp 162−163 °C (hexane/AcOEt); IR ν 1695 cm^{-1}; ^{1}H NMR δ 1.09 (t, J = 7.3 Hz, 3H), 2.23 (s, 3H), 2.46 (q, J = 7.3 Hz, 2H), 3.82 (dd, J = 14.5, 1.7 Hz, 1H), 4.30 (dd, J = 14.5, 4.0 Hz, 1H), 4.80 (d, J = 14.8 Hz, 1H), 4.88 (d, J = 14.8 Hz, 1H), 5.75 (s, 1H), 5.79 (br s, 1H), 6.97−7.20 (m, 5H), 7.54 (br t, J = 7.6 Hz, 1H), 7.71 (br t, J = 7.6 Hz, 1H), 7.80 (br d, J = 7.9 Hz, 1H), 7.93 (s, 1H), 8.03 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 8.2, 16.5, 37.3, 38.3, 53.2, 63.5, 125.9, 126.3, 127.2, 128.0, 128.2, 129.1, 129.2, 129.5, 130.0, 130.1, 130.9, 136.5, 147.7, 148.8, 160.5, 171.2, 202.1. Anal. Calcd for $C_{25}H_{24}N_2O_2S$: C, 72.09; H, 5.81; N, 6.73. Found: C, 72.16; H, 5.88; N, 6.66.

7-(2-Methyl-4-oxohex-2-enoyl)-6,8-dihydro-6-(phenylsulfinylmethyl)pyrrolo[3,4-*b*]quinoline (37). To a solution of **36** (100 mg, 0.240 mmol) in CH_2Cl_2 (12 mL) was added dropwise a solution of MCPBA (56.9 mg, 0.264 mmol) in

CH_2Cl_2 (12 mL) at 0 °C over a period of 30 min. An aqueous $Na_2S_2O_3$ solution (15 mL) was added to the reaction mixture, and the whole was extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$), and concenrated. The residue was chromatographed on silica gel (hexane/AcOEt, 1:4) to give **37** (101.8 mg, 98%): IR ν 1695, 1645 cm^{-1}; ^1H NMR for one diasteromer δ 1.15 (t, J = 7.3 Hz, 3H), 2.46 (d, J = 1.3 Hz, 3H), 2.62 (q, J = 7.3 Hz, 2H), 3.72 (dd, J = 13.5, 3.0 Hz, 1H), 3.97 (dd, J = 13.5, 6.6 Hz, 1H), 5.00 (d, J = 14.5 Hz, 1H), 5.26 (d, J = 14.5 Hz, 1H), 5.84 (dd, J = 6.6, 3.0 Hz, 1H), 6.54 (br s, 1H), 7.42−7.58 (m, 6H), 7.71 (t, J = 6.9 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 8.00 (d, J = 9.6 Hz, 1H), 8.04 (s, 1H); ^1H NMR for the other diasteromer δ 1.14 (t, J = 7.3 Hz, 3H), 2.41 (d, J = 1.7 Hz, 3H), 2.62 (q, J = 7.3 Hz, 2H), 3.49 (dd, J = 13.7, 3.5 Hz, 1H), 4.08 (dd, J = 13.5, 3.0 Hz, 1H), 4.94 (d, J = 15.5 Hz, 1H), 5.26 (d, J = 14.5 Hz, 1H), 5.91 (br t, J = 3.0 Hz, 1H), 6.63 (br s, 1H), 7.41−7.85 (m, 11H). These sulfoxides were used immediately in the next step.

7-(2-Methyl-4-oxohex-2-enoyl)-6,8-dihydro-6-methylenepyrrolo[3,4-*b*]quinoline (38). A mixtue of $CaCO_3$ (58 mg) in toluene (20 mL) was heated under reflux with a Dean−Stark water separator to remove water for 2 h. To this mixture was added a solution of **37** (50.0 mg, 0.16 mmol) in toluene (5 mL), and the mixture was further heated under reflux for 13 h. After the reaction mixture was cooled, $CaCO_3$ was filtered off and the filtrate was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 3:1) to give **38** (17.8 mg, 63%): IR ν 1750 cm^{-1}; ^1H NMR δ 1.13 (t, J = 7.3 Hz, 3H), 2.42 (s, 3H), 2.58 (q, J = 7.3 Hz, 2H), 5.02 (s, 2H), 6.03 (br s, 1H), 6.35 (s, 1H), 7.55 (t, J = 7.3 Hz, 1H), 7.73 (br t, J = 7.3 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 8.05 (s, 1H), 8.12 (d, J = 9.2 Hz, 1H) (the signal for 1H was not detected); ^{13}C NMR δ 7.7, 16.1, 37.9, 51.2, 125.6, 125.7, 126.5, 126.9, 127.8, 128.2, 129.6, 129.9, 130.0, 142.2, 148.0, 148.7, 154.4, 170.2, 201.6; HRMS calcd for $C_{19}H_{18}N_2O_2$ (M^+) 306.1369, found 306.1371.

Mappicine Ketone (1). A solution of **38** (10.0 mg, 0.033 mmol) in MeOH (6.5 mL) was irradiated with a low-pressure mercury lamp (20 w) in a quartz vessel at room temperature for 1.5 h. The reaction mixture was concentrated, and the residue was chromatographed on silica gel (hexane/AcOEt, 1:2) to remove the starting material **38** (3.8 mg). The crude cyclization product **39** was dissolved in acetic acid (2.0 mL) containing 10% Pd/C (1.0 mg), and the mixture was heated at 80 °C for 3 h. Pd/C was filtered off using Celite; the filtrate was poured into a saturated aqueous $NaHCO_3$ solution, and the whole was extracted with AcOEt. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated, and the residue was chromatographed on silica gel (hexane/AcOEt, 1:2) to give **1** (2.8 mg, 28%): mp 235−237 °C (MeOH) (lit.[4a] mp 236−237 °C); IR ν 1710, 1655, 1600 cm^{-1}; ^1H NMR δ 1.25 (t, J = 7.3 Hz, 3H), 2.30 (s, 3H), 2.91 (q, J = 7.3 Hz, 2H), 5.30 (s, 2H), 7.25 (s, 1H), 7.64 (t, J = 7.3 Hz, 1H), 7.81 (t, J = 7.3 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H), 8.35 (s, 1H); ^{13}C NMR δ 7.8, 13.7, 36.0, 50.2, 97.9, 127.1, 127.7, 128.0, 128.2, 128.6, 129.6, 130.5, 131.0, 143.4, 148.2, 148.8, 152.9, 161.8, 205.5; HRMS calcd for $C_{19}H_{16}N_2O_2$ (M^+) 304.1212, found 304.1217.

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Supporting Information Available: ^1H NMR spectra for **7a**, **15**, **20**, **24**, **27**, **30**, **31**, **38**, and mappicine ketone (**1**) and ^{13}C NMR spectra for **7a**, **15**, **24**, **38**, and mappicine ketone (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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