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Synthesis Studies toward Chloroazaphilone and Vinylogous γ-Pyridones: Two Common Natural Product Core Structures

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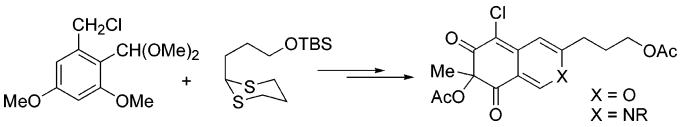
Received March 4, 2005



Chloroazaphilone is a common structure found in a number of natural products. Reported herein is a practical synthesis of a model chloroazaphilone that utilizes $Pb(OAc)_4$ oxidation of $HClO_4$/HOAc pyrinium salt in a key one-pot operation. Reaction of this chloroazaphilone with various primary amines to afford the corresponding vinylogous γ-pyridones was also fully investigated. The isolation of stable enamine intermediates provided direct evidence of reaction mechanisms.

Introduction

Azaphilones are a representative class of natural products derived from pyranoquinone-containing fungal metabolites. These agents exhibit high affinity for ammonia and other amines, resulting in the formation of vinylogous γ-pyridones.[1] Despite the recognized affinity of azaphilone for nitrogen, it was not until 1995 that the first naturally occurring nitrogen-containing derivative, isochromophilone VI, was isolated.[2] To date, several naturally occurring members of this class have been reported that appear to be biogenetically derived from azaphilone common precursors (Figure 1).[3] Among these are those that have a chlorine atom at the C-5 ring position. Azaphilones have been reported to exhibit a wide range of biological activities, including monamine oxidase inhibition,[3b] tumor promotion inhibition,[4] gp120-CD4 binding inhibition,[5] and acyl-CoA:cholesterol acyltransferase (ACAT) inhibition.[6] Although the SAR of azaphilones and their mechanisms of action remain unclear, the potent biological activities of these natural products is thought to be related to the reaction of their 4*H*-pyran nucleus with amines to generate the corresponding vinylogous γ-pyridones.[7] Their reactive nature has made these deceptively simple-looking structures challenging synthesis targets.

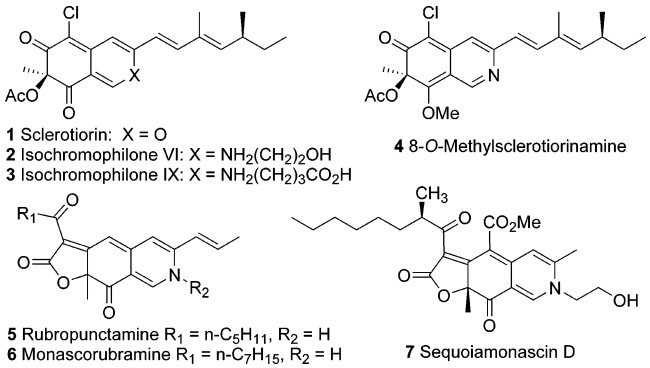


FIGURE 1. Examples of naturally occurring nitrogen-containing azaphilones.

Structurally, azaphilones are featured with a highly oxygenated bicyclic core and a quaternary carbon center.[8] Though a number of synthetic efforts have been made,[9] great challenges remain to construct this structure

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(1) (a) Fujimoto, H.; Matsudo, T.; Yamaguchi, A.; Yamazaki, M. *Heterocycles* **1990**, *30*, 607. (b) Powell, A. D. G.; Robertson, A.; Whalley, W. B. *Chem. Soc. (London), Spec. Publ.* **1956**, *5*, 27. (c) Lin, T. F.; Yakushijin, K.; Buchi, G. H.; Demain, A. L. *J. Ind. Microbiol.* **1992**, *9*, 173.

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(3) (a) Nam, J.-Y.; Kim, H.-K.; Kwon, J.-Y.; Han, M. Y.; Son, K.-H.; Lee, U. C.; Choi, J.-D.; Kwon, B.-M. *J. Nat. Prod.* **2000**, *63*, 1303. (b) Michael, A. P.; Grace, E. J.; Kotiw, M.; Barrow, R. A. *Aust. J. Chem.* **2003**, *56*, 13. (c) Sweeny, J. G.; Estrada-Valdes, M. C.; Iacobucci, G. A.; Sato, H.; Sakamura, S. *J. Agric. Food Chem.* **1981**, *29*, 1189. (d) Stierle, D. B.; Stierle, A. A.; Bugni, T. *J. Org. Chem.* **2003**, *68*, 4966.

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(6) Arai, N.; Shiomi, K.; Tomoda, H.; Tabata, N.; Yang, D.-J.; Masuma, R.; Kawakubo, T.; Omura, S. *J. Antibiot.* **1995**, *48*, 696.

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10.1021/jo050414g CCC: $30.25
Published on Web 04/19/2005

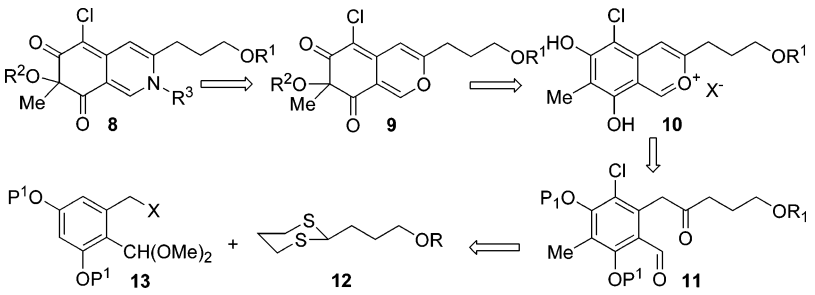
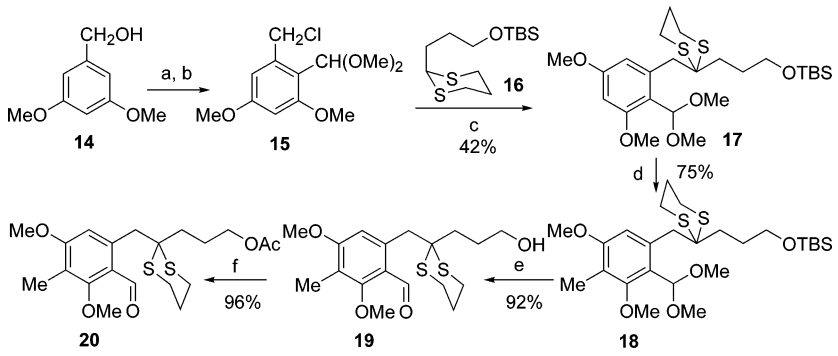


FIGURE 2. Retrosynthetic analysis of chloroazaphilone **9**.

SCHEME 1. Synthesis of the Functionalized Intermediate 20[a]



[a] Reagents and conditions: (a) DMF, $POCl_3$ 60 °C, 87%; (b) $CH(OMe)_3$, *p*-TsOH, MeOH, MS 4 Å, 50 °C, 95%; (c) **16**, *n*-BuLi, THF, −78 to −20 °C, then **15**, 42%; (d) *n*-BuLi, THF, MeI, −78 to −10 °C, 75%; (e) 1 N HCl, acetone, 92%; (f) Ac_2O, Et_3N, CH_2Cl_2, DMAP (cat.), 96%.

efficiently. Recently, Porco's group reported a novel Au(III)-catalyzed cycloisomerization of *o*-alkynylbenzyl aldehydes into 2-benzopyrylium salts and subsequent IBX oxidation to form the azaphilone ring system.[10] In the present paper, we report a practical method to elaborate a model compound, chloroazaphilone **9**, as part of our ongoing efforts toward the total synthesis of structurally related natural products.[11] We have also investigated the reactions of chloroazaphilone **9** with various primary amines. These reactions are shown to prove efficient and concise accesses to the corresponding vinylogous γ-pyridones **8** (Figure 2). The current work supports the previously suggested molecular mode of action of azaphilones wherein they react with the proteins by covalently modifying primary amines of amino acid residues.

Results and Discussion

In our retrosynthetic analysis for the core structure of azaphilone as outlined in Figure 2, the chloroazaphilone **9** is prepared by oxidation of the corresponding 2-benzyzopyrylium salts, which are derived from the formyl ketones **11**.[8d] A potential problem of this oxidation is its requirement for multistep operations and low yield for the key oxidation step. We envisioned a facile route to the stable key intermediate, formyl ketone **11**, through the convergent coupling of appropriately substituted benzylic halides **13** with masked acyllithium dithians **12** followed by suitable protecting group adjustment. Vinylogous γ-pyridone **8** could be derived through treatment of isochromene **9** with a primary amine.

To prepare intermediate **18** (Scheme 1), a preformed side chain was conveniently introduced via the functionalized dithian **16** in a multistep fashion.[12] The synthesis began with the readily available benzyl alcohol **14**. Generation of the dithiane anion of **16** using *n*-BuLi in THF followed by condensation with benzyl chloride **15** afforded intermediate **17** in moderate yield. Selective *n*-BuLi-mediated metalation of the phenyl ring of **17** at the C-3 position followed by in situ treatment with methyl iodide introduced a methyl substituent, affording the fully protected intermediate **18** in satisfactory yield. Protecting group compatibility and their selective removal could potentially prove problematic in subsequent steps, and a variety of different protecting groups were

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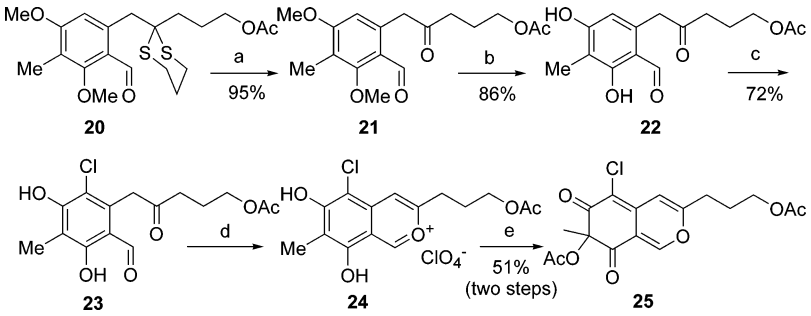
(12) Wei, W. G.; Yao, Z. J. *Tetrahedron* **2003**, *69*, 6621.

SCHEME 2. Practical Synthesis of Chloroazaphilone 25[a]



[a] Reagents and conditions: (a) $Hg(OAc)_2$, CH_3CN-H_2O (v/v 4:1), 95%; (b) $AlCl_3$, CH_2Cl_2, reflux, 86%; (c) SO_2Cl_2, CH_2Cl_2, 72%; (d) HOAc, $HClO_4$, rt, 1 h; (e) HOAc, $Pb(OAc)_4$, rt, 51% (over two steps).

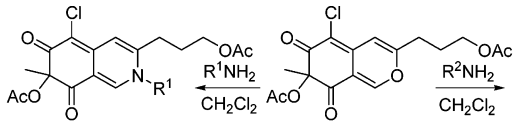
examined. Treatment of the resultant intermediate **18** with 1 N HCl in acetone resulted in complete removal of the dimethyl acetal and silyl ether group. To simplify the following transformations, the newly exposed primary hydroxyl group was reprotected as the acetate **20**.

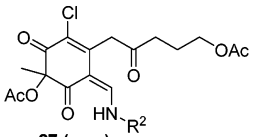
Elaboration of chloroazaphilone **25** is illustrated in Scheme 2. The dithiane moiety was first removed by treatment with $Hg(OAc)_2$ at ambient temperature, yielding formyl ketone **21**. The phenolic methyl ethers were subsequently efficiently deprotected using anhydrous $AlCl_3$ in refluxing CH_2Cl_2 to afford resorcinol derivative **22**. Prior to forming the azaphilone nucleus,[13] a chlorine substituent was introduced at the C-5 position of compound **22**. Chlorination was carried out using SO_2Cl_2 in dichloromethane to afford the formyl ketone **23** in 72% yield. Oxidative transformation of **23** to chloroazaphilone **25** was examined next. Earlier studies on the formation of benzopyrylium salts have generally involved use of HCl(g), P_2O_5, concd H_2SO_4, etc. combined with appropriate solvents under harsh reaction conditions.[9d,14] However, after examining alternative conditions for the formation of pyrylium salts, the use of $HClO_4$ in acetic acid was found to be the best choice both in terms of ease of use and chemical yield. Exposure of formyl ketone **23** to $HClO_4$ in acetic acid at room temperature yielded the intermediate pyrylium salt **24**, which without characterization was oxidized with lead tetraacetate in one pot to afford chloroazaphilone **25** in satisfactory yield (51% over two steps). This one-pot procedure greatly simplifies the synthesis and is highly reproducible, allowing us to prepare **25** on multigram scale to meet the demand for further synthetic investigations. To the best of our knowledge, the one-pot subsequent application of $HClO_4$/HOAc and $Pb(OAc)_4$ is new and represents a convenient entry to the azaphilone nucleus.

With the chloroazaphilone **25** in hand, it was possible to investigate its reaction with various primary amines bearing different substitutions on their α-carbons. The results are shown in Table 1. With less bulky amines, the reaction cleanly afforded the corresponding vinylogous γ-pyridones **26** (a−i), while for bulky amines, such as *tert*-butylamine, the reaction stopped at an intermediate stage and gave stable enamines **27** (a−c).

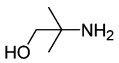
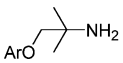
Most of the less bulky primary amines (entries 1−6) reacted with chloroazaphilone **25** to give a deep-red solution, and all products were purified by silica gel chromatography, affording the corresponding vinylogous γ-pyridones in excellent yields. When using L-(−)-γ-methylbenzylamine (entry 7), two diastereomers were separated by flash chromatography, thereby providing facile access to the enantio-pure chloroazaphilones. With more bulky amines (entries 7 and 8), the reaction

TABLE 1. Reactions of Chloroazaphilone 25 with Primary Amines[a]





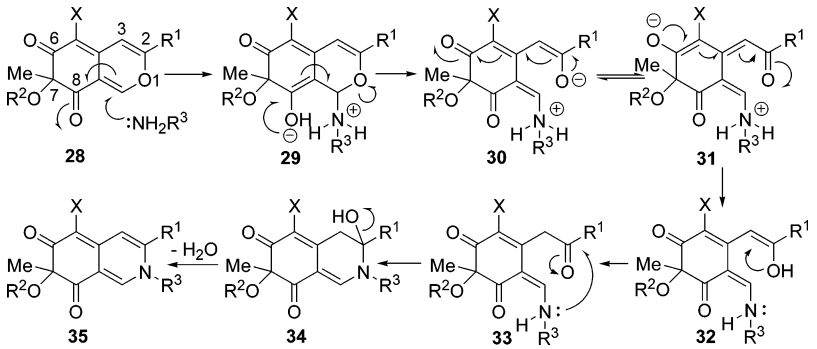
27 (a - c)

Entry	Amine	Time (min)	Product	Yield (%)
1	$NH_3 \bullet H_2O$	1	**26a**	98
2	$MeNH_2$	1	**26b**	98
3	H_2N⁄⁄OH	2	**26c**	96
4	Gly-OMe	2	**26d**	95
5	$BnNH_2$	1	**26e**	97
6		3	**26f**	98
7[b]		60	**26g** and **26h**	44 and 47
8	$PhNH_2$	1 day	**26i**	98
9	*t*-$BuNH_2$	5	**27a**	97
10		5	**27b**	97
11[c]		5	**27c**	95

[a] The reactions were carried out as follows: Substrate **25** (0.1 mmol) in dichloromethane (5 mL) was treated with amines (0.11 mmol) at room temperature. After the starting material had been consumed according to TLC, the solvent was evaporated and the crude products were purified directly by silica gel column chromatography. [b] Two diastereomers (**26h** and **26i**) were isolated, and their absolute stereochemistries were not determined here. [c] Ar = *p*-bromobenzoyl.

(13) Gray, R. W.; Whalley, W. B. *J. Chem. Soc. C* **1971**, 3575.
(14) Chong, R.; King, R. R.; Whalley, W. B. *J. Chem. Soc., Chem. Commun*. **1969**, 1512.

SCHEME 3. Proposed Mechanism for the Reaction of Azaphilone with Primary Amines



solutions usually became deep-yellow initially, but changed to deep-red with prolonged reaction time. In the case of benzylamine (entry 8), TLC showed formation of a new intermediate, which was different from the former vinylogous γ-pyridones. However, it remained stable for a limited time. We envisioned that these reactions proceeded in a multistep process, which could stop at an intermediate stage when reacting with more bulky primary amines, such as *tert*-butylamine (entry 9), 2-amino-2-methyl-1-propanol (entry 10), and 1-aryloxymethyl-1,1-dimethylmethamine (entry 11). This explanation was confirmed by our isolation of a stable enamine **27c** (entry 11) and its unambiguous characterization by single-crystal X-ray analysis (see the Supporting Information).

Early in 1999, a possible mechanism for this reaction was proposed by Tomoda's group in the course of their investigation of bioactivity of azaphilones.[15] Our results cast new insight into the mechanistic aspects of this reaction, wherein the pyranyl oxygen is replaced with nitrogen by insertion of a primary amine. A possible mechanism is now proposed as shown in Scheme 3. Michael addition of a nucleophilic primary amine to the electrophilic C-10 carbon results in the formation of carbinolamine **29** which undergoes C−O bond cleavage to generate enamines **30** and **31**. An intramolecular proton transfer from nitrogen to oxygen gives enamine **32** followed by **33**. Nucleophilic attack on the C-2 carbonyl by the lone electron pair of enamines **33** results in the formation of **34**, which undergoes dehydration to give the nitrogen-containing azaphilone adducts **35**. This mechanistic rationalization was based on the stable enamines **33** isolated when the R^3 group was bulky. Such a reaction mechanism is also consistent with the molecular mode of action of azaphilones in biological contexts.

Conclusion

In summary, a new and practical synthesis of chloroazaphilone and vinylogous γ-pyridones, which represent common key structure cores of a class of bioactive natural products, was developed. The facile methodology provides an important entrance to these structurally related natural products. Reaction of chloroazaphilone with various primary amines was also investigated, where the capture of stable intermediates provided direct evidence on reaction mechanisms. An asymmetric synthesis of azaphilones as well as the synthesis of structurally related natural products is currently ongoing in our laboratory.

Experimental Section

6-[2-(3-Hydroxypropyl)[1,3]dithian-2-ylmethyl]-2,4-dimethoxy-3-methylbenzaldehyde (19). To a solution of **18** (8.7 g, 16.5 mmol) in acetone (20 mL) was added 1 N HCl (10 mL), and the mixture was stirred at room temperature for 4 h. After removal of acetone, the residue was diluted with ethyl acetate (150 mL). The organic layer was washed with water and brine and concentrated to dryness. The oil residue was purified by flash column chromatography on silica gel to give **19** as a colorless oil (5.6 g, 92%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.37 (s, 1H), 6.83 (s, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 3.74 (s, 2H), 3.64 (t, 2H, J = 6.3 Hz), 2.89−2.74 (m, 4H), 2.30 (brs, 1H), 2.14 (s, 3H), 2.05−1.80 (m, 6H); EIMS *m/z* 353 (M − OH); IR (KBr) ν_{max} 3440, 2941, 1737, 1679, 1597, 1567, 1128, 1049 cm^{-1}. Anal. Calcd for $C_{18}H_{26}O_4S_2$: C, 58.35; H, 7.07. Found: C, 58.45; H, 7.21.

Acetic Acid 3-[2-(2-Formyl-3,5-dimethoxy-4-methylbenzyl)[1,3]dithian-2-yl]propyl Ester (20). To a solution of alcohol **19** (5.6 g, 15.2 mmol) and DMAP (cat.) in anhydrous CH_2Cl_2 (50 mL) were added Et_3N (30.5 mL) and Ac_2O (22.8 mL) at 0 °C. The mixture was stirred at room temperature for 2 h, poured into H_2O (30 mL), and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel to afford **20** as a white solid (6.0 g, 96%): mp 77−79 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.38 (s, 1H), 6.81 (s, 1H), 4.05 (t, 2H, J = 6.3 Hz), 3.91 (s, 3H), 3.80 (s, 3H), 3.75 (s, 2H), 2.86−2.77 (m, 4H), 2.15 (s, 3H), 2.04 (s, 3H), 1.95−1.88 (m, 6H); IR (KBr) ν_{max} 2947, 1741, 1672, 1597, 1565, 1387, 1245, 1130, 1057, 779 cm^{-1}; EIMS *m/z* 305 (M^+ − 107). Anal. Calcd for $C_{20}H_{28}O_5S_2$: C, 58.22; H, 6.84. Found: C, 58.29; H, 6.96.

Acetic Acid 5-(2-Formyl-3,5-dimethoxy-4-methylphenyl)-4-oxopentyl Ester (21). To a solution of aldehyde **20** (6.0 g, 14.5 mmol) in CH_3CN/H_2O (40 mL, v/v, 4:1) was added $Hg(OAc)_2$ (11.5 g, 36.3 mmol) in small portions. After being stirred at rt for 30 min, the suspension was filtered through a pad of Celite and washed with ethyl acetate. The filtrate was concentrated to dryness and purified by flash column chromatography on silica gel to yield a white solid (4.8 g, 95%): mp 55−56 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.28 (s, 1H), 6.44 (s, 1H), 4.10 (t, 2H, J = 6.3 Hz), 4.02 (s, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 2.75 (t, 2H, J = 7.5 Hz), 2.14 (s, 3H), 2.06 (s, 3H), 2.05−1.93 (m, 2H); IR (KBr) ν_{max} 2945, 1739, 1712, 1675, 1602, 1568, 1386, 1130, 522 cm^{-1}; EIMS *m/z* 322 (M^+). Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.35; H, 7.04.

Acetic Acid 5-(2-Formyl-3,5-dihydroxy-4-methylphenyl)-4-oxopentyl Ester (22). To a suspension of anhydrous

(15) Tomoda, H.; Matsushima, C.; Tabata, N.; Namatame, I.; Tanaka, H.; Bamberger, M. J.; Arai, H.; Fukazawa, M.; Inoue, K.; Omura, S. *J. Antibiot.* **1999**, *52*, 160.

$AlCl_3$ (8.3 g, 125 mmol) in dry CH_2Cl_2 (80 mL) was added a solution of the formyl ketone **21** (4.0 g, 12.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The resulting mixture was refluxed for 10 h and then poured into ice-cold water. Small portions of MeOH were added to dissolve the solid remaining in the reaction bottle. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried and concentrated. Recrystallization of the solid residue from ethyl acetate and hexane provided **22** as pale crystals (3.2 g, 86%): mp 119−120 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.66 (s, 1H), 9.88 (s, 1H), 6.55 (brs, 1H), 6.20 (s, 1H), 4.08 (t, 2H, J = 6.3 Hz), 3.92 (s, 2H), 2.62 (t, 2H, J = 6.9 Hz), 2.09 (s, 3H), 2.07 (s, 3H), 2.04−1.89 (m, 2H); IR (KBr) ν_{max} 3445, 2903, 1710, 1616, 1583, 1305, 1159, 1031, 832, 570 cm^{-1}; EIMS *m/z* 294 (M^+). Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 61.27; H, 6.06.

Acetic Acid 5-(2-Chloro-6-formyl-3,5-dihydroxy-4-methylphenyl)-4-oxopentyl Ester (23). To a suspension of compound **22** (10.0 g, 34.0 mmol) in anhydrous CH_2Cl_2 (150 mL) was added SO_2Cl_2 (3.2 mL, 40.0 mmol) dropwise at 0 °C. The mixture was warmed to room temperature for 10 min, poured into ice-cold brine, and extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed with H_2O and brine, dried (Na_2SO_4), filtered, and concentrated. The resulting solid was recrystallized from hexane and ethyl acetate to yield **23** as a pale solid (8.0 g, 72%): mp 124−126 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.65 (s, 1H), 9.90 (s, 1H), 6.40 (s, 1H), 4.22 (s, 2H), 4.13 (t, 2H, J = 6.3 Hz), 2.72 (t, 2H, J = 7.1 Hz), 2.20 (s, 3H), 2.10 (s, 3H), 2.00 (m, 2H); IR (KBr) ν_{max} 3340, 2928, 1737, 1709, 1616, 1461, 1251, 1125, 783, 597 cm^{-1}; EIMS *m/z* 328 (M^+).Anal. Calcd for $C_{15}H_{17}ClO_6$: C, 54.84; H, 5.21. Found: C, 54.74; H, 5.32.

Acetic Acid 3-(3-Acetoxypropyl)-5-chloro-7-methyl-6,8-dioxo-7,8-dihydro-6*H*-isochromen-7-yl Ester (25). To a suspension of formyl aldehyde **23** (200 mg, 0.61 mmol) in HOAc (4.0 mL) was added cold $HClO_4$ (2.0 mL) dropwise under N_2. The resulting mixture was stirred at room temperature for 2 h and then treated with $Pb(OAc)_4$ (350 mg, 0.80 mmol). After being stirred for 2.5 h at room temperature, the reaction mixture was quenched by adding ethylene glycol (0.2 mL), diluted with brine, and extracted with ethyl acetate (4 × 15 mL). The combined organic phases were washed with H_2O (20 mL), satd $NaHCO_3$ (15 mL), and brine, dried over Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel to afford **25** as a yellowish solid (115 mg, 51%): mp 177−178 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 (s, 1H), 6.63 (s, 1H), 4.16 (t, 2H, J = 6.0 Hz), 2.62 (t, 2H, J = 7.5 Hz), 2.17 (s, 3H), 2.08 (s, 3H), 2.05−2.00 (m, 2H), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.5, 186.2, 170.8, 170.0, 162.9, 152.9, 138.0, 114.9, 110.7, 106.2, 84.5, 62.8, 30.2, 25.7, 22.2, 20.8, 19.9; IR (KBr) ν_{max} 1737, 1642, 1580, 1538, 1370, 1248, 1128, 1047, 879, 837 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{17}ClO_7$ 368.0663 (M^+), found 368.0711.

General Procedure for the Synthesis of 26a−i and 27a−c. A solution of substrate **25** (0.1 mmol, 1.0 equiv) in dichloromethane (5 mL) was treated with amine (1.1 equiv) at ambient temperature. After the completion of the reaction, the solvent was removed under reduced pressure, and the residue was purified directly by flash chromatography on silica gel. The isolated yields are shown in Table 1 of the text.

Acetic acid 3-(3-acetoxypropyl)-5-chloro-7-methyl-6,8-dioxo-2,6,7,8-tetrahydroisoquinolin-7-yl ester (26a): orange solid; mp 198−200 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (1H, s), 6.87 (1H, s), 4.15 (2H, t, J = 6.2 Hz), 2.74 (2H, t, J = 7.5 Hz), 2.18 (3H, s), 2.09 (3H, s), 2.10−2.04 (2H, m), 1.58 (3H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 193.2, 184.2, 171.1, 170.2, 151.6, 148.6, 138.6, 115.4, 112.4, 100.4, 84.7, 63.0, 30.1, 27.4, 23.4, 20.8, 20.3; IR (KBr) ν_{max} 3214, 3086, 2959, 1745, 1647, 1600, 1558, 1472, 1367, 1241, 1223, 852, 772, 451 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{17}H_{18}ClNO_6$ (M^+) 367.0823, found 367.0833.

Acetic acid 3-(7-acetoxy-5-chloro-2,7-dimethyl-6,8-dioxo-2,6,7,8-tetrahydroisoquinolin-3-yl)propyl ester (26b): orange solid; mp 187−189 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (1H, s), 6.71 (1H, s), 4.14 (2H, t, J = 6.0 Hz), 3.57 (3H, s), 2.62 (2H, t, J = 7.8 Hz), 2.11 (3H, s), 2.04 (3H, s), 2.02−1.94 (2H, m), 1.47 (3H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 193.5, 184.5, 170.8, 170.0, 149.9, 144.3, 142.2, 114.7, 113.0, 101.8, 84.8, 62.8, 41.0, 28.8, 26.8, 23.0, 20.8, 20.2; IR (KBr) ν_{max} 1733, 1705, 1652, 1611, 1508, 1368, 1250, 1212, 1084, 854, 502 cm^{-1}; HRMS *m/z* (EI) calcd for $C_{18}H_{20}ClNO_6$ (M^+ + H) 382.1052, found 382.1048.

Acetic acid 3-(3-acetoxypropyl)-5-chloro-2-(3-hydroxypropyl)-7-methyl-6,8-dioxo-2,6,7,8-tetrahydroisoquinolin-7-yl ester (26c): orange solid; mp 168−169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (1H, s), 6.79 (1H, s), 4.20 (2H, t, J = 6.0 Hz), 4.02 (2H, t, J = 7.5 Hz), 3.73 (2H, t, J = 5.4 Hz), 2.74 (2H, t, J = 5.1 Hz), 2.18 (3H, s), 2.10 (3H, s), 2.07−1.96 (4H, m), 1.54 (3H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 193.5, 184.3, 170.9, 170.0, 150.1, 144.8, 141.3, 114.8, 113.4, 101.1, 84.4, 62.5, 57.0, 49.7, 32.5, 27.9, 27.1, 22.5, 20.2, 19.5; IR (KBr) ν_{max} 3466, 1741, 1592, 1503, 1247, 1223, 1049, 914, 730, 503 cm^{-1}; HRMS *m/z* (EI) calcd for $C_{20}H_{24}ClNO_7$ (M^+ + H) 426.1314, found 426.1297.

[7-Acetoxy-3-(3-acetoxypropyl)-5-chloro-7-methyl-6,8-dioxo-7,8-dihydro-6*H*-isoquinolin-2-yl]acetic acid methyl ester (26d): reddish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (1H, s), 6.76 (1H, s), 4.57 (2H, dd, J_1 = 18.0 Hz, J_2 = 28.2 Hz), 4.17 (2H, t, J = 6.0 Hz), 3.86 (3H, s), 2.54 (2H, t, J = 8.0 Hz), 2.17 (3H, s), 2.10 (3H, s), 2.05−1.97 (2H, m), 1.55 (3H, s); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 193.4, 185.0, 170.8, 170.1, 166.9, 148.8, 143.5, 142.0, 115.1, 113.0, 103.8, 84.9, 62.7, 53.5, 53.4, 28.4, 27.1, 23.0, 20.8, 20.2; IR (KBr) ν_{max} 2959, 1739, 1613, 1511, 1369, 1232, 1085, 1043, 859 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{20}H_{22}ClNO_8$ 439.1034 (M^+), found 439.1004.

Acetic acid 3-(3-acetoxypropyl)-2-benzyl-5-chloro-7-methyl-6,8-dioxo-2,6,7,8-tetrahydroisoquinolin-7-yl ester (26e): orange crystal; mp 154−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (1H, s), 7.47−7.39 (3H, m), 7.27 (2H, d, J = 8.1 Hz), 6.81 (1H, s), 5.05 (2H, s), 4.11 (2H, t, J = 6.0 Hz), 2.58 (2H, t, J = 7.8 Hz), 2.17 (3H, s), 2.03 (3H, s), 2.00−1.90 (2H, m), 1.56 (3H, s); IR (KBr) ν_{max} 1729, 1617, 1513, 1368, 1234, 1143, 1085, 855, 735 cm^{-1}; EI-MS *m/z* 457 (M^+), 415 (M^+ − 42). Anal. Calcd for $C_{24}H_{24}ClNO_6$: C, 62.95; H, 5.28; N, 3.06. Found: C, 62.80; H, 5.29; N, 3.00.

Acetic acid 3-(3-acetoxypropyl)-5-chloro-2-isopropyl-7-methyl-6,8-dioxo-2,6,7,8-tetrahydroisoquinolin-7-yl ester (26f): orange solid; mp 180−183 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (1H, s), 6.77 (1H, s), 4.48−4.39 (1H, m), 4.21 (2H, t, J = 6.0 Hz), 2.72 (2H, t, J = 7.8 Hz), 2.18 (3H, s), 2.10 (3H, s), 2.05−1.99 (2H, s), 1.55 (3H, s), 1.51 (3H, d, J = 4.2 Hz), 1.49 (3H, d, J = 4.2 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 193.3, 184.2, 170.3, 169.7, 148.5, 143.5, 136.0 (2C), 115.2, 113.4, 84.3, 62.4, 51.4, 28.7, 27.3, 22.63, 22.56, 22.3, 20.4, 19.8; IR (KBr) ν_{max} 1738, 1609, 1504, 1368, 1247, 1142, 1083, 1042, 851, 775 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}ClNO_6$ 410.1365 (M^+), found 410.1388.

Compound 26g: reddish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.44−7.17 (m, 5H), 6.81 (s, 1H), 5.45 (q, 1H, J = 6.9 Hz), 4.17 (t, 2H, J = 6.0 Hz), 2.72−2.66 (m, 2H), 2.16 (s, 3H), 2.07 (s, 3H), 2.04−1.98 (m, 2H), 1.85 (d, 3H, J = 6.6 Hz), 1.53 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 193.2, 184.4, 169.78, 169.74, 149.1, 143.3, 138.4, 137.5, 129.2 (2C), 128.6, 125.5 (2C), 114.8, 113.5, 102.1, 84.3, 62.4, 58.6, 28.6, 27.3, 22.6, 20.9, 20.4, 19.8; IR (KBr) ν_{max} 2983, 1738, 1707, 1647, 1612, 1508, 1367, 1251, 1143, 1084, 1044, 854, 701 cm^{-1}; HRMS *m/z* (ESI) calcd for $C_{25}H_{26}ClNO_6$ (M^+ + H) 472.1521, found 472.1524.

Compound 26h: reddish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.46−7.40 (m, 3H), 7.19 (d, 2H, J = 8.1 Hz), 6.80 (s, 1H), 5.46 (q, 1H, J = 6.9 Hz), 4.17 (t, 2H, J = 6.0 Hz), 2.76−2.67 (m, 2H), 2.16 (s, 3H), 2.07 (s, 3H), 2.08−2.04 (m, 2H), 1.86 (d, 3H, J = 6.6 Hz), 1.55 (s, 3H); ^{13}C NMR (75.0 MHz,

$CDCl_3$) δ 193.1, 184.3, 170.3, 169.6, 149.1, 143.3, 137.9, 137.4, 129.3 (2C), 128.6, 125.6 (2C), 114.9, 113.4, 102.2, 84.5, 62.4, 58.7, 28.6, 27.3, 22.7, 21.2, 20.4, 19.8; IR (KBr) ν_{max} 2928, 1738, 1707, 1613, 1508, 1367, 1249, 1143, 1084, 854, 701 cm^{-1}; HRMS *m/z* (ESI) calcd for $C_{25}H_{26}ClNO_6$ (M^+ + H) 472.1521, found 472.1524.

Acetic acid 3-(7-acetoxy-5-chloro-7-methyl-6,8-dioxo-2-phenyl-2,6,7,8-tetrahydroisoquinolin-3-yl)propyl ester (26i): orange needles; mp 213−215 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.60−7.58 (m, 2H), 7.33−7.27 (m, 3H), 6.87 (s, 1H), 3.96 (t, 2H, J = 6.0 Hz), 2.41 (t, 2H, J = 7.8 Hz), 2.18 (s, 3H), 1.96 (s, 3H), 1.83−1.78 (m, 2H), 1.58 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 193.2, 184.7, 170.2, 169.8, 149.0, 143.3, 140.9, 139.7, 130.0 (3C), 126.3, 114.0, 112.4 (2C), 103.2, 84.3, 62.3, 29.0, 26.9, 22.5, 20.3, 19.8; IR (KBr) ν_{max} 1736, 1704, 1614, 1589, 1490, 1368, 1279, 1251, 1207, 1033 cm^{-1}; HRMS *m/z* (ESI) calcd for $C_{23}H_{22}ClNO_6$ (M^+ + H) 444.1208, found 444.1202.

Acetic acid 4-(5-acetoxy-2-oxopentyl)-5-(*tert*-butylaminomethylene)-3-chloro-1-methyl-2,6-dioxocyclohex-3-enyl ester (27a): yellow crystal; mp 95−96 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, 1H, J = 13.2 Hz), 7.76 (d, 1H, J = 15.6 Hz), 4.06 (t, 2H, J = 6.0 Hz), 3.94 (s, 2H), 2.68 (t, 2H, J = 6.9 Hz), 2.18 (s, 3H), 2.03 (s, 3H), 1.93−1.88 (m, 2H), 1.55 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 204.8, 193.5, 188.0, 171.1, 169.4, 151.7, 146.7, 118.0, 100.9, 83.3, 62.6, 54.2, 45.5, 37.7, 29.2 (3C), 23.4, 22.2, 20.4, 19.7; IR (KBr) ν_{max} 2980, 1735, 1682, 1636, 1596, 1542, 1363, 1342, 1249, 1194, 1138, 1040, 827 cm^{-1}; HRMS *m/z* (ESI) calcd for $C_{21}H_{29}ClNO_7$ (M^+ + H) 442.1627, found 442.1631.

Acetic acid 4-(5-acetoxy-2-oxopentyl)-3-chloro-5-[(2-hydroxy-1,1-dimethylethylamino)methylene]-1-methyl-2,6-dioxocyclohex-3-enyl ester (27b): yellow solid; mp 125−126 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.00 (d, 1H, J = 14.1 Hz), 7.76 (d, 1H, J = 14.4 Hz), 4.08−4.00 (m, 2H), 4.02−3.86 (m, 2H), 3.54 (s, 2H), 2.67 (t, 2H, J = 6.8 Hz), 2.17 (s, 3H), 2.04 (s, 3H), 1.96−1.88 (m, 2H), 1.55 (s, 3H), 1.291 (s, 3H), 1.288 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 204.8, 193.6, 188.1, 171.2, 169.5, 152.6, 146.9, 118.1, 101.1, 83.3, 69.4, 62.7, 57.2, 45.6, 37.4, 23.9, 23.4, 23.3, 22.0, 20.4, 19.7; IR (KBr) ν_{max} 3385, 1733, 1712, 1681, 1637, 1553, 1272, 1249, 1204, 1056, 827; HRMS *m/z* (ESI) calcd for $C_{21}H_{28}ClNO_8$ (M^+ + H) 458.1576, found 458.1574.

4-Bromobenzoic acid 2-{[5-acetoxy-2-(5-acetoxy-2-oxopentyl)-3-chloro-5-methyl-4,6-dioxocyclohex-2-enylidenemethyl]amino}-2-methylpropyl ester (27c): yellow solid; mp 111−112 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 11.17 (d, 1H, J = 13.5 Hz), 7.92 (d, 2H, J = 7.0 Hz), 7.81 (d, 1H, J = 13.8 Hz), 7.61 (d, 2H, J = 7.0 Hz), 4.27 (s, 2H), 4.07−4.01 (m, 2H), 3.89 (s, 2H), 2.65 (d, 2H, J = 6.9 Hz), 2.17 (s, 3H), 2.02 (s, 3H), 1.91−1.85 (m, 2H), 1.52 (s, 3H), 1.49 (s, 6H); IR (KBr) ν_{max} 2958, 1718, 1629, 1543, 1332, 1275, 1241, 1105, 1047, 823, 759 cm^{-1}; MALDI-FTMS (DHB) *m/z* 662 (M^+ + Na).

Acknowledgment. This work was financially supported by the Major State Basic Research and Development Program (G2000077500), NSFC (20432020, 20425205 and 20321202), the Chinese Academy of Sciences (KGCX2-SW-209), and Shanghai Municipal Commission of Science and Technology (04DZ14901). We thank Dr. Terrence R. Burke, Jr., for helpful comments.

Supporting Information Available: General experimental procedures, copies of ^1H NMR spectra for compounds **19**−**23**, **25**, **26a**−**i**, and **27a**−**c**, and copies of ^{13}C NMR spectra for compounds **25**, **26a**−**d**, **26f**−**i**, and **27a**,**b**, as well as crystallographic data for compound **27c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO050414G