REACTIONS OF 1*H*-2,3-DIKETOPYRIDO[4,3,2-*de*] QUINOLINE WITH ACETONE AND ACETOPHENONE: A NOVEL SYNTHESIS OF THE ISOQUINOLINO[6,5,4,3-*cde*]QUINOLINE NUCLEUS

Qizhu Ding and J. William Lown*

Department of Chemistry,
University of Alberta, Edmonton, Alberta, Canada, T6G 2G2

Abstract: The reaction of 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline **1** with two equivalents of acetone or acetophenone led to the formation of 4-methylisoquinolino[6,5,4,3-*cde*]quinoline **2** and 4-phenylisoquinolino[6,5,4,3-*cde*]quinoline **9**, respectively. Mechanistic examination shows that **1** reacted with acetone first to form the intermediates, **5a** and **5b**. Intermediates **5a** and **5b** were then dehydrated to form a intermediate **12** which reacted with another acetone molecule to produce the intermediate **14**. Finally, the intermediate **14** cyclized via a 1,6-cyclization reaction and aromatized via 1,2-elimination reaction to produce the tetracyclic compound **2**. The structures of the intermediates **5a** and **5b** were established by HRMS, ^{1}HNMR, as well as by x-ray diffraction analysis. The reaction between **1** and acetone-d_6 was studied and the resulting product 1*H*-2-keto-3,5-dideuterio-4-trideuteriomethyl-6-chloro-8,9-dimethoxyisoquinolino[6,5,4,3-*cde*]quinoline **4** was obtained. Acetophenone also reacts with **1** to produce the final product **9** via a similar mechanism. Two ethoxycarbonylmethyl derivatives from **2** and **9** were synthesized and their structures were characterized by HRMS, ^{1}HNMR as well as by NOE measurements.

Introduction

In recent years, much attention has been focused upon the isolation and structure determination of biologically active materials from marine sources. Heterocycloquinoline groups exist in many marine products. The pyrrolo[4,3,2-*de*]quinoline ring system was first recognized as a component of these marine products. These include discorhabdins (1), makaluvamines (2), batzellines (3), isobatzellines (4), and damirones (2c, 5). These alkaloids have provided a useful source of possible pharmaceutical analogs. A broad range of biological activities have been shown to exist, these include *in vivo* and *in vitro* cytotoxicity against several tumor cell lines (2, 6), topoisomerase I inhibition (2b, 6f, 7) and topoisomerase II inhibition(2b, 6f, 7, 8). For instance, from their first isolation the discorhabdin alkaloids have proven to be one of the most biologically active natural products from this family of closely related marine metabolites. Discorhabdin D showed very potent cytotoxicities against the murine P388 leukemia cell line (*in vivo* and *in vitro*), and discorhabdin A against human colon tumor cell HCT-116 (6k). Makaluvamines show cytotoxicity towards several tumor cell lines (2a). Biophysical studies of the makaluvamines have shown that they intercalate into DNA and cause DNA single-strand breakage under the

reductive conditions (2a, 9). The most active (toxic) makaluvamines are those that intercalate well into DNA and also have the highest redox potential. The newest alkaloids to date, veiutamine, wayakin and tsitsikammamine show important biological activities (10). As a consequence of these developments, many research groups are currently interested in the synthetic chemistry of these heterocycloquinoline compounds (6h, 6k, 11).

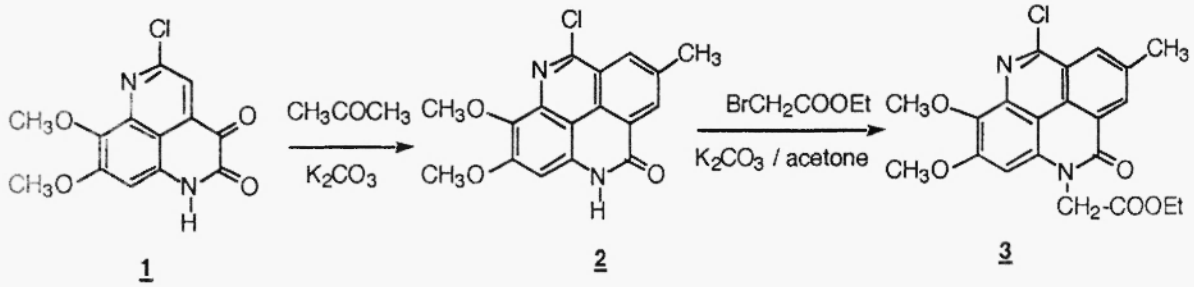
Another class of marine products containing the pyrido[4,3,2-*de*]quinoline nucleus was also isolated from sponges and other marine sources. Most of these compounds show *in vitro* cytotoxicity against tumor cells in culture (L1210 murine leukemia, P388, etc.). The mechanistic studies show that they are DNA intercalating agents . Amphimedine (12), isolated from a sponge, was active against P338 cells *in vitro* (Ed50 2.8 μg/mL). 2-Bromoleptoclinidone (13), isolated from an ascidian, also active against P338 leukemia cells *in vitro* and with higher activity (ED50 0.4 μg/mL). Dercitin inhibits a variety of cultured cell clones at nanomolar concentrations and shows antitumor activity in mice and modest antiviral activity against herpes simplex and A-59 murine corona viruses at micromolar concentration (14). The synthetic chemistry and physiological properties of this kind of pyrido[4,3,2-*de*]quinoline nucleus and its derivatives have been therefore the focus of several recent studies (15).

Recently we have synthesized a series of heterocycloquinolines such as pyrrolo[4,3,2-*de*]quinolines (6j, 16), furo[4,3,2-*de*]quinoline (17) and pyrido[4,3,2-*de*]quinoline(18). All of these compounds exhibit high cytotoxicities. 1*H*-2,3-diketo-5-chloro-7,8-dimethoxypyrido[4,3,2-*de*]quinoline **1** has high cytotoxic potency and this compound can react with acetone to produce a nucleophilic addition product, 1*H*-2-keto-3-hydroxy-3-acetylmethyl-5-chloro-7,8-dimethoxypyrido[4,3,2-*de*]quinoline. Our continuing interesting in the reactivity of the 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline led us to study this novel reaction and the synthesis of isoquinolino[6,5,4,3-*cde*]quinolines from 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline. We describe herein the reactions between 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline and acetone as well as acetophenone and an efficient synthesis of the novel isoquinolino[6,5,4,3-*cde*]quinoline nucleus.

Results and Discussion

The reaction of 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline **1** with acetone in the presence of K_2CO_3 at refluxing temperature for 12 hrs led to the formation of the isoquinolino[6,5,4,3-*cde*]quinoline **2** in 85% yield (Scheme 1).

Scheme 1



1 **2** **3**

Structural elucidation was based on spectroscopic data and deuterium replacement. Thus the HRMS spectrum of **2** shows a molecular ion m/z: 328.0616 (100%), which corresponds to the formula of $C_{17}H_{13}N_2O_3Cl$ (calcd: 328.0615). The intensity of the molecular ion is 100% which implies that the ring system of compound **2** is quite stable. The ^{1}HNMR spectrum of **2** in DMSO-d_6 shows two new protons at 8.56 and 8.49 ppm as well as signals in the aromatic region and a new methyl group at 2.74 ppm. Compound **2** also exhibits strong fluorescence.

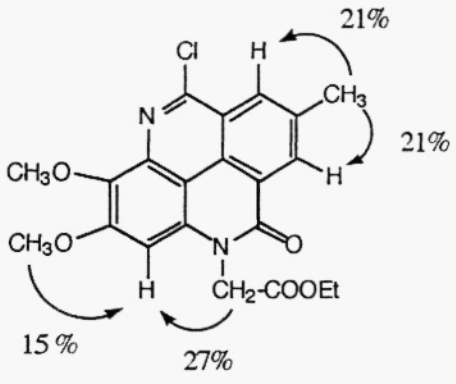


Figure 1 The NOE results of **3** in $CDCl_3$

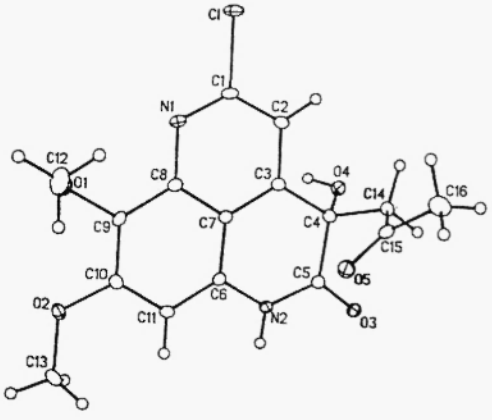
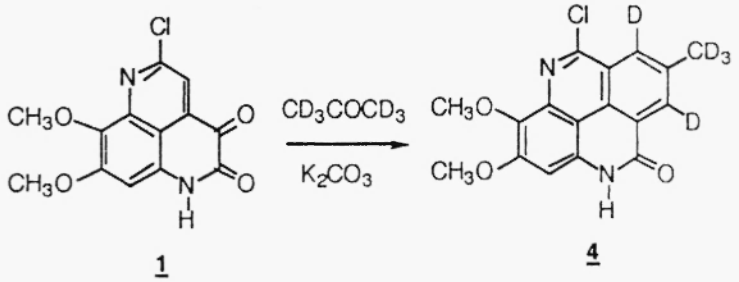


Figure 2. ORTEP diagram of intermediate 5b with the non-hydrogen atoms represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

In order to further confirm the structure of compound **2**, a derivative, 1-ethoxycarbonylmethyl-2-keto-4-methyl-6-chloro-8,9-dimethoxyisoquinolino[6,5,4,3-*cde*]quinoline **3**, was synthesized. The HRMS of **3** shows a molecular ion m/z: 414.0975, which corresponds to the formula of $C_{21}H_{19}N_2O_5Cl$ (calcd: 414.0982). The NOE results show the correct relationships of 9-CH_3O / 10-H, N-CH_2 / 10-H, 4-CH_3 / 3-H and 4-CH_3 / 5-H (see Fig. 1). In order to understand the mechanism of the reaction between pyrido[4,3,2-*de*]quinoline **1** and acetone, a deuterium replacement experiment was carried out. Acetone-d_6 was allowed to react with 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline **1** under the same conditions as those used in the synthesis of compound **2**. The final product was purified and identified as 1*H*-2-keto-3,5-dideuterio-4-trideuteriomethyl-6-chloro-8,9-dimethoxyisoquinolino[6,5,4,3-*cde*]quinoline **4** (Scheme 2).

Scheme 2



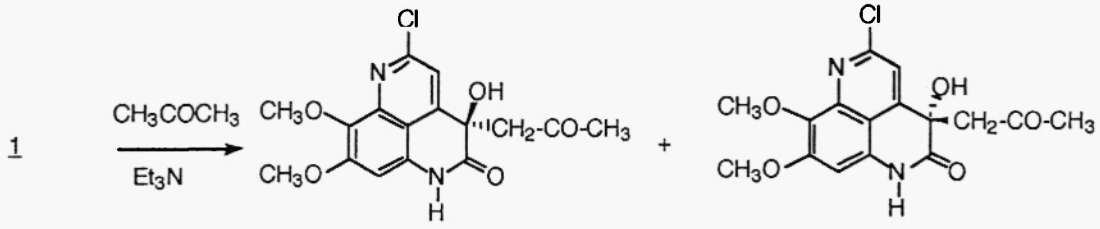
1 **4**

The HRMS spectrum of **4** shows a molecular ion m/z: 333.0928 (100%), which corresponds to the formula of $C_{17}H_8D_5N_2O_3Cl$ (calcd: 333.0929). Comparing with compound **2**, 5 protons were replaced by 5 deuterium atoms in the product. ^{1}HNMR of **4** shows that two aromatic protons at 8.56 and 8.49 ppm and three methyl protons at 2.74 ppm have been removed. The number of carbon atoms in compound **4** is 17, but the total carbon in compound **1** and acetone-d_6 is only 16. It is evident that if the 3-CD came from the first reactant acetone-d_6, the 5-CD should come from the second acetone-d_6 equivalent.

In the reaction leading to the formation of compound **2**, an intermediate was found in the first 30 minutes which is a highly fluorescent compound. This intermediate was isolated by column chromatography and characterized by ^{1}HNMR, HRMS and x-ray diffraction. The HRMS spectrum shows a molecular ion m/z at 350.0666 (76.2%) which corresponds to the formula of $C_{16}H_{15}N_2O_5Cl$ (calcd: 350.0669). The ^{1}HNMR spectrum in DMSO-d_6 shows an exchangeable proton at 6.59 ppm, which corresponds to a hydroxy group, and three protons at 2.01 ppm, which corresponds to a methyl group. An αα splitting of CH_2 protons was found in the range of 3.6 to 3.8 ppm (CH_2-Ha 3.72 ppm, CH_2-Hb 3.68 ppm, J = 17 Hz) which suggests that these two protons on CH_2 group have different chemical environments. Another active proton appears at 10.85 ppm which corresponds to the N-H of the 1*H*-2-keto pyridine skeleton.

The results of x-ray diffraction show that this intermediate is a mixture of (R)-1*H*-2-keto-3-hydroxy-3-acetylmethyl-5-chloro-7,8-dimethoxy[4,3,2-*de*]quinoline **5a** and (S)-1*H*-2-keto-3-hydroxy-3-acetylmethyl-5-chloro-7,8-dimethoxy[4,3,2-*de*]quinoline **5b** (see Figure 2). Acetone first takes part in a nucleophilic addition on the 3-carbonyl group in the formation of **2** (Scheme 3). The intermediates **5a** and **5b** can also be synthesized by the catalytic reaction of Et_3N instead of K_2CO_3 at room temperature. This makes it more convenient to isolate the intermediates.

Scheme 3

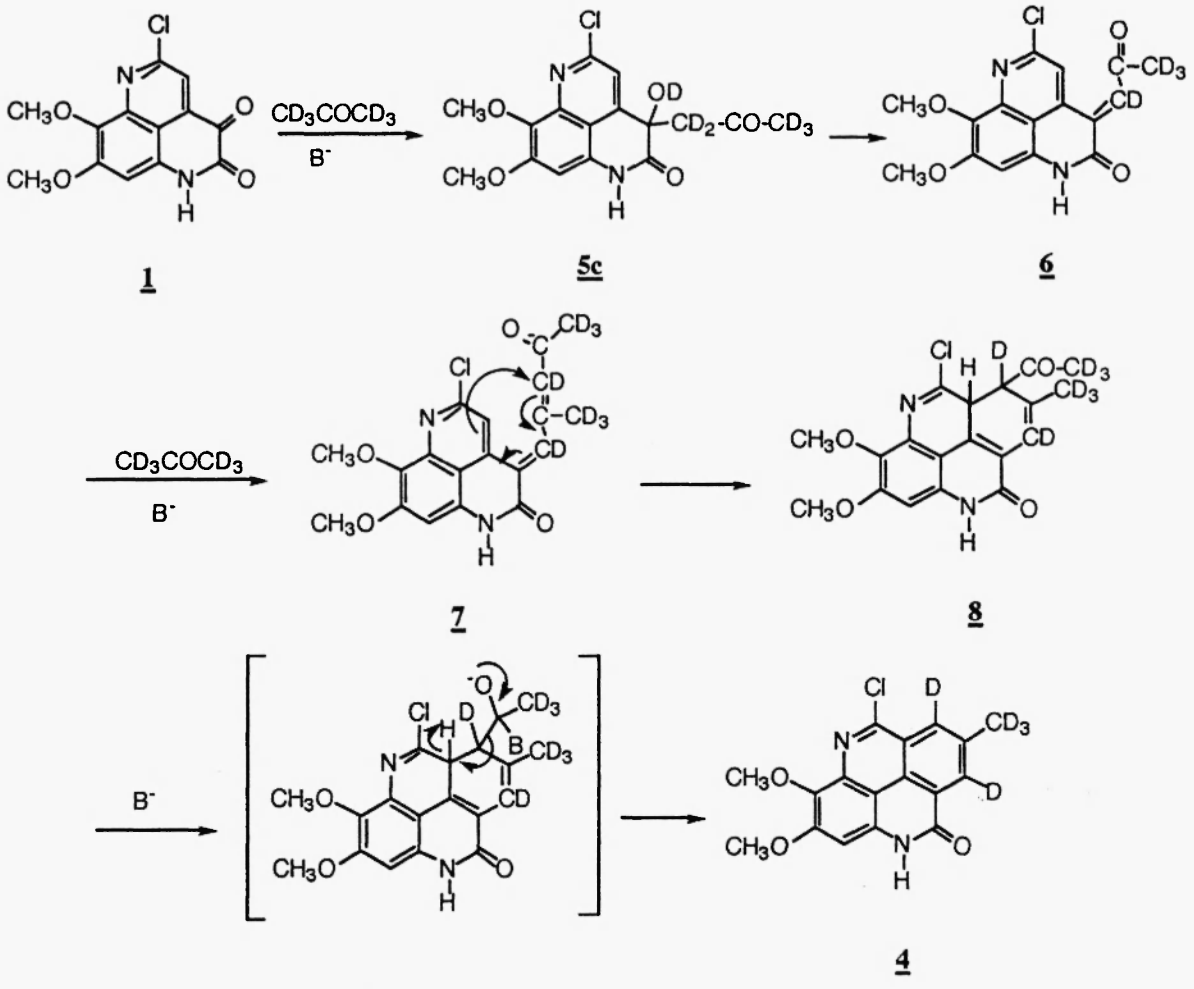


5a **5b**

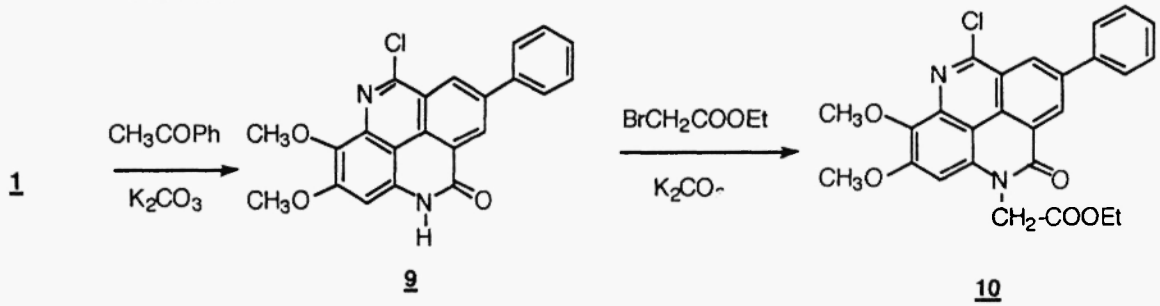
According to the results from the intermediates and the experiment involving deuterium replacement, a mechanism for the formation of isoquinolino[6,5,4,3-*cde*]quinoline **4** can be logically proposed as shown in scheme 4. In the presence of base, compound **1** reacts with acetone-d_6 first to form the nucleophilic addition product **5c**, which loses a D_2O to produce the intermediate **6**. Intermediate **6** reacts with another acetone-d_6 to form the intermediate **7**, then **7** takes part in an 1,6-cyclization addition to produce the intermediate **8** which is aromatized *via* an 1,2-elimination reaction to afford the final product 1*H*-2-keto-3,5-dideuterio-4-trideuteriomethyl-6-chloro-8,9-dimethoxyisoquinolino[6,5,4,3-*cde*]quinoline **4**.

Acetophenone can also react similarly with 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline **1** to form the 4-phenylisoquinolino[6,5,4,3-*cde*]quinoline **9** (Scheme 5). An ethoxycarbonylmethyl derivative **10** was synthesized directly from **9** or from **1** in an one-pot process. The NOE results are shown in Figure 3.

Scheme 4



Scheme 5



An intermediate **11** was also isolated during the course of the reaction. In the HRMS of **11**, the molecular ion at m/z 412.0826 was not observed, but the fragment of M - acetophenone at m/z 292.0247 (100%) is prominent which corresponds to the formula of $C_{13}H_9N_2O_4Cl$ (calcd: 292.0251). This result suggests that intermediate **11** readily loses an acetophenone moiety to regenerate the starting material 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline **1**. This elimination reaction was also observed in methanolic solutions of **11**. In the ^{1}HNMR of **11** in $CDCl_3$, the αα splitting can also be observed in the range of 3.7 to 4.2 ppm (J = 16.9 Hz) which corresponds to the two environmentally different protons on the CH_2 group (CH_2-Ha, 4.08 ppm; CH_2-Hb, 3.87 ppm). The structure of intermediate **11** was further characterized by x-ray diffraction analysis. The results of x-ray diffraction show that the intermediate **11** is a R/S diastereomeric mixture of (R)-1*H*-2-keto-3-hydroxy-3-benzoylmethyl-5-chloro-7,8-dimethoxypyrido[4,3,2-de]quinoline **11a** and (S)-1*H*-2-keto-3-hydroxy-3-benzoylmethyl-5-chloro-7,8-dimethoxypyrido[4,3,2-de]quinoline **11b** (see Figure 4).

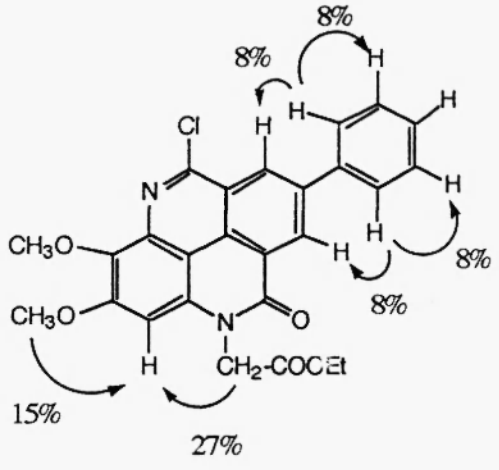


Figure 3 The NOE results of **10** in $CDCl_3$

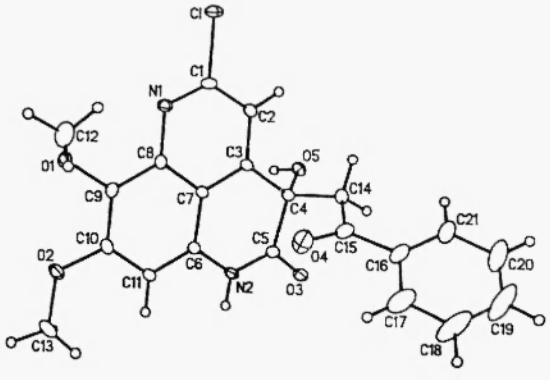
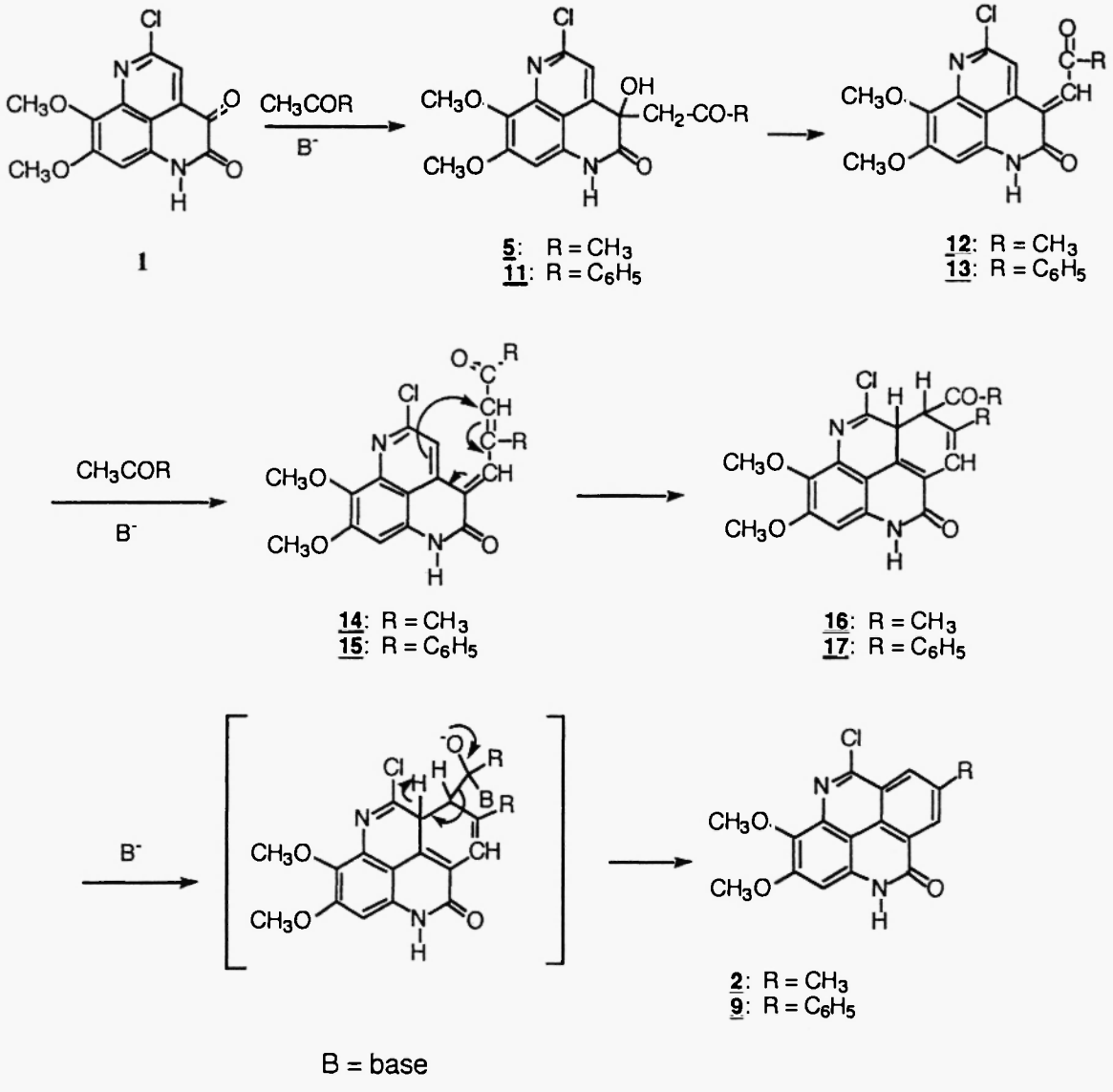


Figure 4. ORTEP diagram of intermediate **11b** with the non-hydrogen atoms represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

Based on above results, a mechanism for the formation of 4-methylisoquinolino[6,5,4,3-*cde*]quinoline **2** and 4-phenylisoquinolino[6,5,4,3-*cde*]quinoline **9** can be proposed as shown in the scheme 6. Three distinct reactions are involved in this mechanism: a. nucleophilic addition; b. 1,6-cyclization addition; c. 1,2-elimination. Exploration of these novel heterocyclic systems is continuing and their biological properties will be reported in due course.

Scheme 6



Experimental Section

Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}HNMR spectra were recorded on a Bruker AM-360 spectrometer. Chemical shifts were measured relative to an internal standard. High resolution mass spectra (HRMS) were recorded on a Kratos AEI MS-9 mass spectrometer and reported as m/z. Analytical thin layer chromatography was performed on silica-coated plastic plates (silica gel 60, F-254, Merck). Preparative separations were performed by flash chromatography on silica gel (Merck, 70-230 or

230-400 mesh). 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline **1** was prepared according to our reported method[18]. Et_3N, K_2CO_3, acetone, acetone-d_6 and acetophenone were commercial reagents and were used as received.

1*H*-2-keto-4-methyl-6-chloro-8,9-dimethoxyisoquinolino[6,5,4,3-*cde*]quinoline (2). A solution of 30 mg of 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline **1** in 20 mL of acetone was treated with 80 mg of K_2CO_3 and refluxed for 12 hrs. After removing the excess of acetone, the residue was purified by chromatography (silica gel, Merck, 230-400 mesh; 4 : 1 of ethyl acetate : hexane then ethyl acetate) to give 28 mg of yellow product of 1*H*-2-keto-4-methyl-6-chloro-8,9-dimethoxyisoquinolino[6,5,4,3-*cde*]quinoline **2**. Yield 85%; m.p >300 °C (undec.). HRMS calc for $C_{17}H_{13}N_2O_3Cl$: 328.0615, found 328.0616 (100%). ^{1}HNMR in DMSO-d_6: δ 12.01 (s, 1 H, NH); 8.56 (m, 1 H, 5-H); 8.49 (m, 1 H, 3-H); 7.34 (s, 1 H, 10-H); 3.98 (s, 3 H, 8-OCH_3); 3.97 (s, 3 H, 9-OCH_3); 2.74 (s, 3 H, 4-CH_3). Anal. calcd for $C_{17}H_{13}N_2O_3Cl$: C, 62.11; H, 3.99; N, 8.52; Cl, 10.78. Found C, 62.37; H, 4.21; N, 8.55; Cl, 10.48.

1-Ethoxycarbonylmethyl-2-keto-4-methyl-6-chloro-8,9-dimethoxyisoquinolino[6,5,4,3-*cde*]quinoline (3). A solution of 20 mg of 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline in 20 mL of acetone was treated with 100 mg of K_2CO_3 and refluxed for 12 hrs. Then the resulting mixture was treated with 100 mg of $BrCH_2COOEt$ and refluxed for another 4 hrs. After removing the excess of acetone, the residue was extracted with chloroform (30 mL x 2) and purified by chromatography (silica gel, Merck, 230-400 mesh; 1 : 1 of ethyl acetate : hexane) to give 22 mg of yellow product of 1-ethoxycarbonylmethyl-2-keto-4-methyl-6-chloro-8,9-dimethoxyisoquinolino[6,5,4,3-*cde*]-quinoline **3**. Yield 78%; m.p 250-2 °C. HRMS calcd for $C_{21}H_{19}N_2O_5Cl$: 414.0982, found 414.0975 (100%). ^{1}HNMR in $CDCl_3$: δ 8.75 (m, 1H, ArH); 8.54 (m, 1 H, ArH); 6.79 (s, 1 H, 10-H); 5.28 (s, 2 H, NCH_2); 4.27 (q, 2 H, J = 7.2 Hz, OCH_2); 4.19 (s, 3H, 8-OCH_3); 4.07 (s, 3 H, 9-OCH_3); 2.79 (s, 3 H, 4-CH_3); 1.28 (t, 3H, J = 7.2 Hz, CH_3). Anal. calcd for $C_{21}H_{19}N_2O_5Cl$: C, 60.80; H 4.62; N, 6.75; Cl, 8.55. Found: C, 60.57; H, 4.78; N, 6.46; Cl, 8.83.

1*H*-2-keto-3,5-dideuterio-4-trideuteriomethyl-6-chloro-8,9-dimethoxyisoquinolino[6,5,4,3-*cde*]quinoline (4). The procedures of synthesis and purification were the same as those used in the synthesis of **2**. Yield 68%; m.p > 300 °C (undec.). HRMS calcd for $C_{17}H_8D_5N_2O_3Cl$: 333.0929, found 333.0928 (100%). ^{1}HNMR in DMSO-d_6: δ 12.05 (s, 1 H, NH); 7.35 (s, 1 H, 10-H); 4.00 (s, 3 H, 8-OCH_3); 3.98 (s, 3 H, 9-OCH_3).

(R/S)-1*H*-2-keto-3-hydroxy-3-acetylmethyl-5-chloro-7,8-dimethoxypyrido[4,3,2-de]quinoline (5). A solution of 20 mg of 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline in 10 mL acetone was treated with 5 drops of triethylamine and stirred at room temperature for 4 hrs. After removing the volatile solvents, 25 mg of **5** as a light yellow product was obtained. This crude product was then purified by chromatography (silica gel, Merck, 230-400 mesh; 4 : 1 of ethyl acetate : hexane then ethyl acetate) to give 18 mg of pure **5**. Yield 75%; m.p 230 °C (dec. to a dark solid). ^{1}HNMR in DMSO-d_6: δ 10.85 (s, 1 H, NH); 7.50 (s, 1 H, 4-H); 6.96 (s, 1 H, 9-H); 6.59 (s, 1 H, 3-OH); 3.93 (s, 3 H, 8-OCH_3); 3.83 (s, 3 H, 9-OCH_3); 3.72 (d, 1 H, J = 17 Hz, CH_2-Ha); 3.68 (d, 1

H, J = 17 Hz, CH_2-Hb). HRMS calcd for $C_{16}H_{15}N_2O_5Cl$: 350.0669, found: 350.0666 (76.2%). Anal. calcd for $C_{16}H_{15}N_2O_5Cl$: C, 54.79; H, 4.31; N, 7.99; Cl, 10.11. Found C, 54.57; H, 4.24; N, 7.88; Cl, 10.28.

1*H*-2-keto-4-phenyl-6-chloro-8,9-dimethoxyisoquinolino[6,5,4,3-cde]quinoline (9). A solution of 30 mg of 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline **1** in 5 g of acetophenone was treated with 80 mg of K_2CO_3 and stirred at 85 C for 24 hrs. The resulting mixture was purified by chromatography (silica gel, Merck, 230-400 mesh; 4 : 1 of ethyl acetate : hexane then ethyl acetate) to give 18 mg of yellow product of 1*H*-2-keto-4-phenyl-6-chloro-8,9-dimethoxyisoquinolino[6,5,4,3-*cde*]quinoline **9**. Yield 45%; m.p > 300 °C (undec.). HRMS calcd for $C_{22}H_{15}N_2O_3Cl$: 390.0771, found 390.0769 (100%). ^{1}HNMR in DMSO-d_6: δ 12.38 (s, 1 H, NH); 8.94 (d, 1 H, J = 1.8 Hz, 5-H); 8.83 (d, 1 H, J = 1.8 Hz, 3-H); 7.94 (d, 2 H, J = 7.2 Hz, o-ArH); 7.61 (t, 2 H, J = 7.2, m-ArH); 7.51 (t, 1 H, J = 7.2, p-ArH); 7.39 (s, 1 H, 10-H; 4.00 (s, 3 H, 8-OCH_3); 3.99 (s, 3 H, 9-OCH_3). Anal. calcd for $C_{22}H_{15}N_2O_3Cl$: C, 67.61; H, 3.87; N, 7.17; Cl, 9.07. Found C, 67.66; H, 3.56; N, 7.32; Cl, 8.73.

1-Ethoxycarbonylmethyl-2-keto-4-phenyl-6-chloro-8,9-dimethoxyisoquinolino[6,5,4,3-cde]quinoline (10). A solution of 20 mg of 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline in 5 g of acetophenone was treated with 100 mg of K_2CO_3 and stirred at 95 °C for 24 hrs. After removing the excess of acetophenone under vacuum, the residue was treated with 20 mL of THF and 100 mg of $BrCH_2COOEt$ and the resulting mixture was refluxed for 5 hrs. After removing the THF in vacuo, the residue was extracted with chloroform (30 mL x 2). The chloroform solution was concentrated and purified by chromatography (silica gel, Merck, 230-400 mesh; 1 : 1 of ethyl acetate : hexane) to give 16 mg of pure product. Yield 49%; m.p 193-5 °C. ^{1}NMR in $CDCl_3$: δ 9.19 (d, 1 H, J = 1.8 Hz, 5-H); 8.95 (d, 1 H, J = 1.8 Hz, 3-H); 7.86 (d, 2 H, J = 7.0 Hz, o-ArH); 7.58 (t, 2 H, J = 7.0 Hz, m-ArH); 7.49 (t, 1 H, J = 7.0 Hz, p-ArH); 7.01 (s, 1 H, 10-H); 5.33 (s, 2 H, NCH_2); 4.29 (q, 2 H, J = 7.2, OCH_2); 4.21 (s, 3 H, 8-OCH_3); 4.09 (s, 3 H, 9-OCH_3); 1.21 (s, 3 H, J = 7.2 Hz, CH_3). HRMS calcd for $C_{26}H_{21}N_2O_5Cl$: 476.1139, found 476.1138. Anal. calcd for $C_{26}H_{21}N_2O_5Cl$: C, 65.48; H, 4.44; N, 5.87; Cl, 7.43. Found C, 65.69; H, 4.21; N, 5.68; Cl, 7.72.

(R/S)-1*H*-2-keto-3-hydroxy-3-benzoylmethyl-5-chloro-7,8-dimethoxypyrido[4,3,2-de]quinoline (11). A solution of 30 mg of 1*H*-2,3-diketopyrido[4,3,2-*de*]quinoline in 0.6 g of acetophenone was treated with 5 drops of triethylamine and the resulting mixture was stirred at room temperature overnight. After purification by chromatography (silica gel, Merck, 230-400 mesh; 4:1 of ethyl acetate : hexane), 30 mg of 1*H*-2-keto-3-hydroxy-3-benzoylmethyl-5-chloro-7,8-dimethoxypyrido[4,3,2-*de*]quinoline **11** was obtained. Yield 70%; m.p 154-5 °C. HRMS calcd for M - $CH_3COC_6H_5$ = 292.0251, found 292.0247 (100%). LRMS: 412.7 (M, 53.8%); 396.8 (M - OH, 12.2%); 292.7 (M - CH_3COPh, 57.6%); 105.0 (PhCO, 100%). ^{1}HNMR in $CDCl_3$: δ 9.51 (s, 1 H, NH); 7.76 (dd, 2 H, J = 8, 1.2 Hz, m-ArH); 7.51 (tt, 1 H, J = 8, 1.2 Hz, p-ArH); 7.36 (dt, 2 H, J = 8, 1.2 Hz, o-ArH); 7.37 (s, 1 H, 4-H); 6.74 (s, 1 H, 9-H); 5.00 (s, 1 H, 3-OH); 4.08 (d, 1 H, J = 16.9 Hz, CH_2-Ha); 3.87 (d, 1 H, J = 16.9 Hz, CH_2-Hb). Anal. calcd for $C_{21}H_{17}N_2O_5Cl$: C, 61.10; H, 4.15; N, 6.79; Cl, 8.59. Found C, 61.43; H, 4.27; N, 6.55; Cl, 8.84.

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