Synthesis and Reactivity of 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole Derivatives, Analogs of the FR900482 and Mitomycin C Active Intermediates

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A series of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles were prepared as analogs of the active intermediates of the natural products, mitomycin C and FR900482, and their reactions with various nucleophiles were studied.

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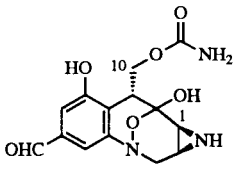
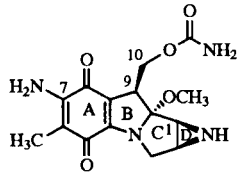
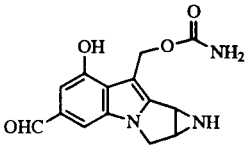
The antitumor antibiotics, FR900482 and mitomycin C, are activated under reductive conditions [1]. Reduction of FR900482's hydroxylamine, followed by the loss of water, is believed to lead to the formation of the active intermediate **1**, which then forms DNA-DNA crosslinks by alkylation at C-1 and C-10 [2]. Reduction of mitomycin C's quinone functionality, followed by the loss of methanol, leads to the structurally similar 7-aminoleucoaziridinomitosene **2** [3]. We proposed to explore the mechanism of action of these natural products by studying the reaction of the active intermediate analog **3** (X and Y are leaving groups) with various nucleophiles, such as potassium ethyl xanthate and 2'-deoxyguanosine.



FR900482



Mitomycin C



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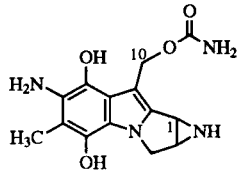

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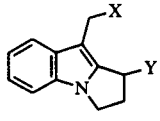


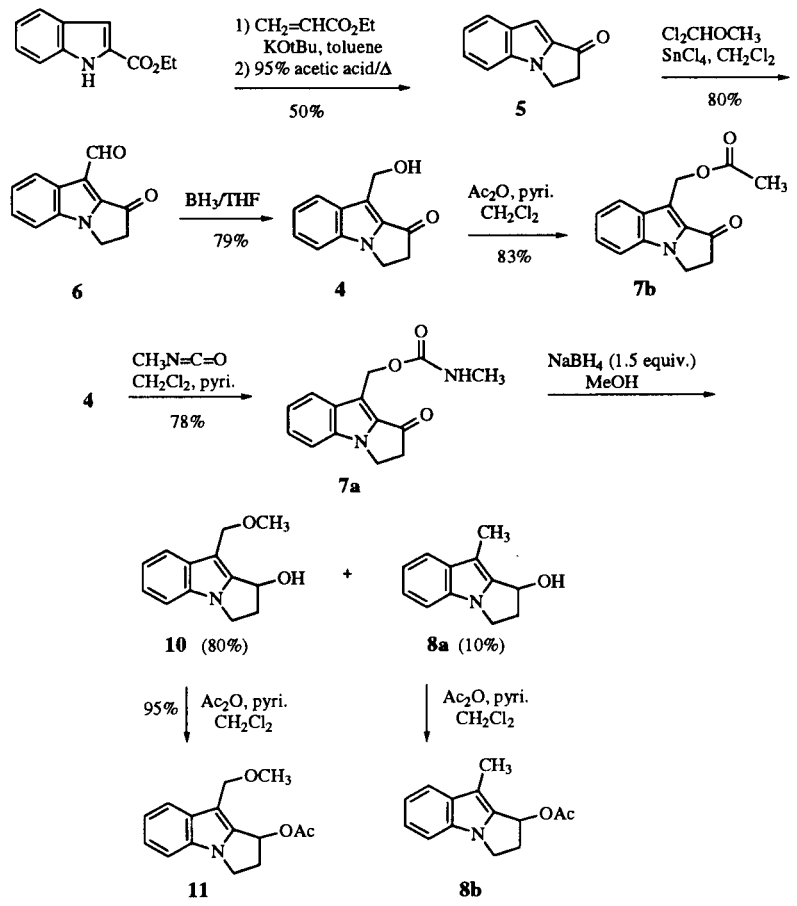
3

An important intermediate in our synthesis of compounds of type **3** is the hydroxy ketone **4** (Scheme 1). The tricyclic ketone **5** was synthesized from ethyl indole-2-carboxylate and ethyl acrylate according to the method of Remers *et al.* [4] in a 40-50% yield, except that toluene was used as a solvent instead of benzene. Formylation of **5** with α,α-dichloromethyl methyl ether and stannic chloride was accomplished in an 80% yield to give **6** [5]. Reduction of **6** with borane allowed the selective reduction of the formyl group in the presence of the keto group to give a 79% yield of **4** [6].

Conversion of a primary alcohol into a carbamoyloxy (O-(C=O)NH_2) group is normally accomplished by a two-step sequence consisting of 1) formation of the phenyl carbonate with phenyl chloroformate, and 2) reaction with ammonia in dichloromethane. We were unable to form the phenyl carbonate under standard conditions, however **4** reacted with excess methyl isocyanate in dichloromethane to give a 78% yield of the methyl carbamate **7a**. Acetylation results in the formation of **7b**. Compounds **7a** and **7b** have a good leaving group at C-10. In order to form another leaving group at C-1, it is necessary to reduce the keto group at C-1 to the alcohol. Initial attempts to reduce either **7a** or **7b** with sodium borohydride in methanol, followed by acetylation of the crude product with acetic anhydride/pyridine resulted in the formation of **8b**. Once the stabilizing electron-withdrawing effect of the keto group is gone, the indole lone pair apparently causes ejection of the carbamoyloxy (or acetyloxy) group at C-10, resulting in the formation of the iminium species **9**. This species then reacts with another hydride equivalent to give the alcohol **8a**, which is then acetylated.

Ketone **7a** was reacted with 1.5 molar equivalents of sodium borohydride in methanol at 0° and the reaction monitored by tlc. Complete disappearance of the starting material occurred after several hours and the solvent was removed *in vacuo* at room temperature. This resulted in a 80% yield of **10** and a 10% yield of **8a**. Similar results were obtained with **7b**. Reaction of **10** with five mole equivalents of sodium borohydride in methanol at 0° for 3 hours, did not lead to the formation of **8a**. The starting material was recovered unchanged. Apparently the iminium species **9**, does not form from **10**. This indicates that, under these conditions, a methoxy group is not a sufficiently good leaving group to lead to the formation of **9**, but that acetyloxy or carbamoyloxy groups are. Once **9** has formed from **7a** or **7b**, reaction with methanol leads to **10** and reaction with excess hydride results in **8a**. Reduction of **7a** with sodium borohydride in tetrahydrofuran at 0° resulted in the formation of **8a**. Attempts to

Scheme 1

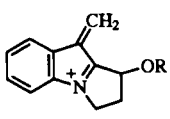


form the corresponding mesylate from **10** were unsuccessful, leading only to decomposition [7]. Acetylation of **10** gives **11**. When a very good leaving group, such as a sulfonate ester, is at position 1, the indolylic nitrogen apparently causes ejection of that group, leading to decomposition products. On the other hand, an acetoxy group at C-1 results in a compound that is sufficiently stable to be isolated.

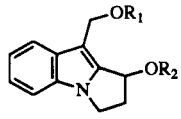
Compounds **10** and **11** were reacted with several different nucleophiles to test the scope of their reactivity. Reaction of **11** with potassium ethyl xanthate in methanol at room temperature results in the formation of **10**. We assume that acetylation of the ethyl xanthate is taking place. This is in contrast to the reaction of potassium ethyl xanthate with mitomycin C [8] or mitosenes [9], in which one or both of the leaving groups at C-1 and C-10 is displaced. Heating **10** at 55-60° with 1.5 equivalents of potassium ethyl xanthate in methanol for 6.5 hours resulted in the formation of several unidentified compounds.

Stirring **11** in perdeuteriomethanol at 55-60° for 16 hours results in the formation of **12a,** while heating in methanol at 55-60° for 12 hours gives complete conversion to **12b**. Allowing **11** to stir in perdeuteriomethanol for 3 days at room temperature, results mostly in unchanged starting material. However, four minor byproducts were characterized by gc-ms: **12a** (m/z 237), **12c** (m/z 234), **12d** (m/z 262), and **17a** (m/z 392) [10]. This suggests that both the iminium species **13** and **14** are intermediates. However, stirring **10** in methanol at 55° for 16 hours gives unchanged starting material. This result indicates that an acetyloxy group at C-1 is displaced by the lone pair on N-4 to form **13**, but that a hydroxy group at C-1 is too poor a leaving group to undergo a similar transformation. Refluxing **10** in perdeuteriomethanol for approximately 24 hours gives a mixture of **10** and **12e**. Heating **12b** in perdeuteriomethanol at 55-60° for 12 hours also leads to a mixture of **12b** and **12f** in its ^{1}H nmr and mass spectra. A peak at m/z 386 in the mass spectrum indicates the formation of a small amount of the dimer **17b**. The rate of exchange at C-10 is apparently slower for **10** and **12b** than for **11**.

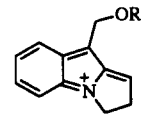
Refluxing **10** or **11** with 2',3',5'-triacetylguanosine in acetonitrile for 4 days gave no reaction. Both starting materials were recovered unchanged. Formation of **13** and **14** appears to take place in the polar, protic solvent, methanol, which stabilizes these ionic species. However,



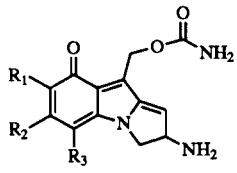
9, R = H
14, R = Ac or CD_3



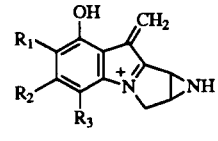
12a, $R_1 = CD_3$, $R_2 = CD_3$
12b, $R_1 = CH_3$, $R_2 = CH_3$
12c, $R_1 = CH_3$, $R_2 = CD_3$
12d, $R_1 = CD_3$, R_2 = Ac
12e, $R_1 = CD_3$, R_2 = H
12f, $R_1 = CD_3$, $R_2 = CH_3$



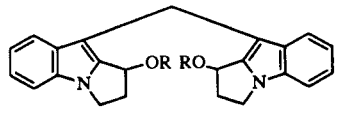
13, R = OCH_3 or OCD_3



15, FR900482: R_1 = H, R_2 = CHO, R_3 = H
Mitomycin C: $R_1 = NH_2$, $R_2 = CH_3$, R_3 = OH



16, FR900482: R_1 = H, R_2 = CHO, R_3 = H
Mitomycin C: $R_1 = NH_2$, $R_2 = CH_3$, R_3 = OH



17a, R = CD_3
17b, R = CH_3

in the less polar, aprotic solvent, acetonitrile, these iminium ions either do not form or form tight ion pairs that collapse back to the neutral compounds without being trapped by other nucleophiles.

The proposed active intermediates for FR900482 and mitomycin C, **1** and **2** respectively, both have an hydroxyl group at C-8. This strongly electron-donating group should favor the formation of **15**. Our results indicate that even in the absence of an electron-donating group at C-8, the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole system can be quite reactive depending on the leaving group ability of the substituent at C-1. Our attempts to form a mesylate at C-1 did not result in an isolable compound. On the other hand, an acetyloxy group was stable at room temperature, but could be displaced at 55-60°, while a hydroxy or methoxy group at C-1 was stable even at 55-60°.

We found that in our 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]-indole system, the substituent at C-10 is replaced more readily than that at C-1, which indicates that **14** is formed more readily than **13**. It is not surprising that **14** is more stable than **13** since the benzene substructure is intact in **14**, whereas in **13** it is not. This is in contrast to mitomycin C, where alkylation occurs more readily at C-1[1a,3a,8,9]. The fused aziridine ring in the mitomycins and FR900482 seems to explain this phenomenon. The aziridine ring is an excellent leaving group, even better than the carbamoyloxy group at C-10. Relief of ring strain favors the formation of **15** over **16**, even though **15** does not contain a benzene ring, while **16** does. Therefore alkylation occurs first at C-1 in the mitomycins and FR900482, followed by expulsion of the carbamoyloxy group, and alkylation at C-10.

EXPERIMENTAL

General.

Elemental analyses were processed by Quantitative Technologies, Inc, Whitehouse, NJ and National Chemical Consulting, Tenafly, NJ. Mass spectra were processed by the University of California Mass Spectroscopy Facility, Riverside, CA and the Center for Advanced Food Technology, Rutgers University, New Brunswick, NJ. Dichloromethane and tetrahydrofuran were distilled from calcium hydride. All nmr spectra were taken on a Varian Gemini 200 MHz nmr spectrometer.

2,3-Dihydro-9-hydroxymethyl-1*H*-pyrrolo[1,2-*a*]indol-1-one (**4**).

A 100-ml, 3-necked round-bottom flask and stir bar were dried in an oven overnight and then allowed to cool to room temperature under a nitrogen atmosphere. A total of 200 mg (1.0 mmole) of **6** and 20 ml dry tetrahydrofuran was then added. The reaction flask was allowed to cool to 0° in an ice bath. A total of 754 µl (0.75 mmole) of 1.0*M* borane in tetrahydrofuran was then added *via* syringe. This was stirred at room temperature for 3 hours (at which time tlc revealed that all of the starting material had disappeared). A total of 40 ml of water was then added and the resulting solution was stirred for 15 hours at room temperature. The solution was then put on a rotary evaporator until most of the tetrahydrofuran was removed. The solution was then extracted three times with dichlorormethane. The combined organic phase was washed twice with 1*N* sodium bicarbonate, dried with magnesium sulfate, and the solvent was evaporated at reduced pressure. The residue was purified by column chromatography (65:35 ethyl acetate:petroleum ether). A total of 150 mg (79%) was obtained. It is important to note that when more than one equivalent of borane was used some of the ketone was also reduced and when 0.5 of an equivalent was used a significant amount of the starting material remained. We found that 0.75 of an equivalent gave the best results, mp 172-174°; ir (potassium bromide): ν 3415 (OH), 1675 (C=O), 1540, 1530, 1565 cm^{-1}; ^1H nmr: δ 3.26 (t, J = 6.2 Hz, 2H), 3.65 (broad s, 1H), 4.46 (t, J = 6.2 Hz, 2H), 5.10 (s, 2H), 7.18-7.32 (m, 1H), 7.40-7.42 (m, 2H), 7.72 (d, J = 8.2 Hz, 1H); ms: m/z 201 (M^+).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.10; H, 5.35; N, 6.84 [11].

9-Formyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (**6**).

A 100-ml, 3-necked round-bottom flask and stirring bar were dried in an oven overnight and then allowed to cool to room temperature under a nitrogen atmosphere. A total of 14 ml (14 mmoles) of tin(IV) chloride (1.0 *M* in dichloromethane) and 842 µl (9.3 mmoles) of dichloromethyl methyl ether were added *via* syringe. The flask was then put into an ice bath and allowed to cool to 0°. A total of 1.20 g (7.0 mmoles) of **5** was dissolved in 50 ml of dry dichlorormethane and was added very slowly (over a 2.5 hour period) to the reaction flask *via* syringe. The reaction mixture was stirred for 4 days at room temperature. A total of 20 ml of water was then added and this was

stirred for 3 hours. The aqueous layer was extracted three times with dichloromethane. The combined organic phase was filtered through Celite, washed twice with 3*N* hydrochloric acid, once with brine, dried over magnesium sulfate, filtered and evaporated *in vacuo* to yield 1.23 g of a brown/black solid. This solid was purified by column chromatography (65:35 ethyl acetate:petroleum ether). An analytical sample was obtained by recrystallizing from dichloromethane and petroleum ether. A total of 1.13 g (80%) was obtained, mp 197-200° dec; ir (potassium bromide): ν 1705 (C=O), 1655, 1540, 1475, 1395, 1300 cm^{-1}; ^1H nmr: δ 3.30 (t, J = 6.0 Hz, 2H), 4.51 (t, J = 6.0 Hz, 2H), 7.37-7.50 (m, 3H), 8.41 (d, J = 7.4 Hz, 1H), 10.43 (s, 1H); ms: m/z 199 (M^+).

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.10; H, 4.44; N, 6.89.

2,3-Dihydro-9-(*N*-methylcarbamoyloxy)methyl-1*H*-pyrrolo-[1,2-*a*]indol-1-one (**7a**).

To a solution of 21 mg (0.1 mmole) of **4** in 5 ml of freshly distilled dichloromethane was added 1.76 ml (200 equivalents) of methyl isocyanate. The reaction mixture was stirred for 3 days at room temperature in a sealed flask. Then 50 ml of both dichloromethane and water were added and the phases were separated. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (65:35 ethyl acetate:petroleum ether) gave 20 mg (78%) of a yellow solid. An analytical sample was prepared by recrystallizing from petroleum ether/dichloromethane, mp, 167-169° dec; ir (potassium bromide): ν 3350, 2940, 1700 (C=O), 1680 (C=O), 1560, 1530, 1395, 1300, 1250 cm^{-1}; ms: m/z 258 (M^+), 201 (M^+-O=C=NCH$_3$); ^1H nmr: δ 2.80 (d, J = 4.8 Hz, 3H), 3.21 (t, J = 6.2 Hz, 2H), 4.40 (t, J = 6.2 Hz, 2H), 4.54-4.78 (broad m, 1H), 5.56 (s, 2H), 7.19-7.26 (m, 1H), 7.38-7.41 (m, 2H), 7.90 (d, J = 8.2 Hz, 1H).

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.03; H, 5.52; N, 10.47.

9-Acetyloxymethyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (**7b**).

A 25-ml, 3-necked round-bottom flask and stir bar were dried in an oven overnight and then allowed to cool to room temperature under a nitrogen atmosphere. A total of 50 mg (0.25 mmole) of **4** and 5 ml of dichloromethane was then added. Next, 101 μl (5 equivalents) of anhydrous pyridine was added *via* syringe. The flask was cooled to 0° with an ice bath and then 47 μl (0.50 mmoles) of acetic anhydride was added *via* syringe. The reaction was stirred at ambient temperature for 24 hours. Starting material was still present by tlc so another 50 μl of acetic anhydride was added *via* syringe. After eight hours, another 50 μl of acetic anhydride and 100 μl of pyridine was added. After another 18 hours, 10 ml of 10% sodium acetate solution was added. The *p*H was around 6, so a little 1*N* sodium bicarbonate was added to raise the *p*H to 7. The phases were separated and the aqueous phase was extracted twice with dichloromethane. The combined organic layer was then washed with brine, dried with magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting yellowish solid was purified on a silica gel column with 3:2 petroleum ether:ethyl acetate. A total of 50 mg (83%) of a white solid was obtained, mp 149-151°; ir (potassium bromide): ν 1710 (C=O), 1685 (C=O), 1570, 1240 cm^{-1}; ms: m/z 243 (M^+), 200 (M^+-C(O)CH$_3$), 184 (M^+-OC(O)CH$_3$); ^1H nmr: δ 2.08 (s, 3H), 3.23 (t, J = 6.2 Hz, 2H), 4.43 (t, J = 6.2 Hz, 2H), 5.57 (s, 2H), 7.20-7.28 (m, 1H), 7.40-7.42 (m, 2H), 7.84 (d, J = 8.2 Hz, 1H).

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.13; H, 5.39; N, 5.76. Found: C, 68.77; H, 5.38; N, 5.55.

2,3-Dihydro-1-hydroxy-9-methoxymethyl-1*H*-pyrrolo[1,2-*a*]-indole (**10**).

A solution of **7a** (100 mg, 0.39 mmole) in 10 ml of methanol was placed into a 50-ml round-bottom flask at 0° (ice-water bath) under nitrogen. To this solution, 22 mg (0.58 mmole) of sodium borohydride was added. The reaction was allowed to stir for three hours until the starting material disappeared according to tlc. To this solution 5 ml of water was added, and then methanol was removed under reduced pressure at room temperature. Dichloromethane was used to extract the product three times. The organic layer was dried over magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure. Purification by silica gel chromatography gave 67 mg (80%) of **10** and 7 mg (10%) of **8a**. Compound **10** had ^1H nmr (deuteriochloroform): δ 2.49-2.65 (m, 1H), 2.82-3.02 (m, 1H), 3.50 (s, 3H), 4.01-4.11 (m, 1H), 4.18-4.30 (m, 1H), 4.77 (s, 2H), 5.40 (dd, J = 3.6, 6.6 Hz, 1H), 7.11-7.29 (m, 3H), 7.65 (d, J = 7.6 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 37.7, 43.1, 58.9, 67.5, 67.6, 104.7, 110.5, 119.6, 120.0, 121.9, 131.6, 132.6, 144.7; ms: m/z 217 (M^+), 186 (M^+-OCH$_3$); hrms: Calcd. for $C_{13}H_{15}NO_2$: 217.1103. Found: 217.1102. Compound **8a** had ^1H nmr (deuteriochloroform): δ 1.79 (broad s, 1H), 2.38 (s, 3H), 2.50-2.59 (m, 1H), 2.78-2.97 (m, 1H), 3.96-4.09 (m, 1H), 4.14-4.26 (m, 1H), 5.38 (d, J = 6.0 Hz, 1H), 7.05-7.23 (m, 3H), 7.56 (d, J = 7.2 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 9.1, 39.2, 42.3, 67.5, 103.6, 110.2, 119.3, 120.0, 122.0, 132.9, 133.2, 142.1; ms: m/z 187 (M^+), 170 (M^+-OH); hrms: Calcd. for $C_{12}H_{13}NO$: 187.0997. Found: 187.0997.

1-Acetyloxy-2,3-dihydro-9-methoxymethyl-1*H*-pyrrolo[1,2-*a*]-indole (**11**).

In a 50-ml round bottom flask, a total of 20 mg (0.077 mmole) of **10** was dissolved in 5 ml of freshly-distilled dichloromethane. The solution was cooled to 0° with a water-ice bath, and 15.7 mg (0.154 mmole) of acetic anhydride was added, followed by 0.1 ml of pyridine. The reaction mixture was stirred at 0° for 2 hours and room temperature for 10 hours. The solution was diluted with dichloromethane, washed once with 1*N* hydrochloric acid, and then twice with water. The organic layer was separated, dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude product was purified by silica gel chromatography (1:1 ethyl acetate:petroleum ether) to give 23 mg (95%) of **11**; ^1H nmr (deuteriochloroform): δ 2.07 (s, 3H), 2.58-2.69 (m, 1H), 2.81-3.09 (m, 1H), 3.37 (s, 3H), 4.07-4.30 (m, 2H), 4.65 (d, J = 11 Hz), 4.72 (d, J = 11 Hz), 6.36 (dd, J = 2, 6.6 Hz, 1H), 7.10-7.31 (m, 3H), 7.71 (d, J = 8.0 Hz, 1H); ^{13}C nmr (deuteriochloroform): δ 21.6, 36.4, 42.7, 58.0, 65.6, 69.0, 106.4, 110.4, 120.3, 120.7, 122.6, 132.3, 133.2, 140.4, 171.0; ms: m/z 259 (M^+), 228 (M^+-OCH$_3$), 200 (M^+-OC(O)CH$_3$).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.49; H, 6.61; N, 5.40. Found: C, 70.06; H, 6.65; N, 5.18 [11].

1-Trideuteriomethoxy-9-trideuteriomethoxymethyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (**12a**).

A total of 43 mg (0.16 mmole) of **11** was dissolved in 1 ml of perdeuteriomethanol in a 25-ml round bottom flask with a condenser. It was stirred at 55-60° for 12 hours. The solvent was then removed *in vacuo* to give a quantitative yield of **12a**; ^{1}H nmr (deuteriochloroform): δ 2.57-2.88 (m, 2H), 3.99-4.10 (m, 1H), 4.15-4.26 (m, 1H), 4.73 (s, 2H), 4.96 (dd, J = 1.8, 3.8 Hz, 1H), 7.08-7.28 (m, 3H), 7.69 (d, J = 7.2 Hz, 1H); ms: m/z 237 (M^+), 203 (M^+-OCD_3).

2,3-Dihydro-1-methoxy-9-methoxymethyl-1*H*-pyrrolo[1,2-*a*]-indole (**12b**).

A total of 15 mg (0.065 mmole) of **11** was stirred in 2 ml of methanol at 55-60° for 12 hours. The solvent was removed under reduced pressure and the quantitative yield of **12b** was obtained; ^{1}H nmr (deuteriochloroform): δ 2.60-2.89 (m, 2H), 3.40 (s, 3H), 3.42 (s, 3H), 4.01-4.30 (m, 2H), 4.73 (s, 2H), 4.97 (d, J = 6.0 Hz, 1H), 7.08-7.27 (m, 3H), 7.70 (d, J = 8.0 Hz, 1H); ms: m/z 231 (M^+), 200 (M^+-OCH_3).

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 73.13; H, 7.50; N, 5.82.

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