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The Preparation of a Hexacyclic Intermediate for the Synthesis of Strychnos Alkaloids

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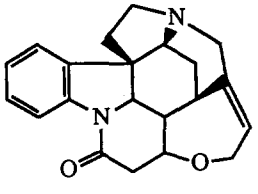
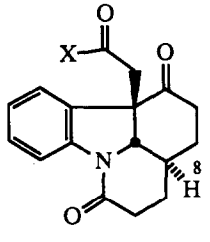
Abstract: Hexacyclic intermediate **17** has been synthesized in nine steps from aldehyde **3**. Key steps include the selective reduction of aldehyde **3**, the stereoselective introduction of an allyl group via the Sakurai reaction and the ozonolysis/dehydrative cyclization to afford bridgehead enamine **17**.

From both a chemical and toxicological perspective, the Strychnos alkaloids have attracted considerable attention over the past three decades.[1,2] Recent syntheses[3] by Magnus, Stork, Kuehne and Overman plus approaches[4] to the Strychnos skeleton by Vollhardt and by Massiot attest to the continuing synthetic interest in the Strychnos skeleton. We previously reported the preparation of an intermediate for the synthesis of Strychnos alkaloids[5]. The key steps in our route were an intramolecular Diels-Alder reaction of a 3-alkenylindole and a Lewis acid-mediated alkylation of a surprisingly unreactive enol silyl ether. We now report the construction of a hexacyclic intermediate containing functionality which may be suitable for conversion into strychnine (**1**).

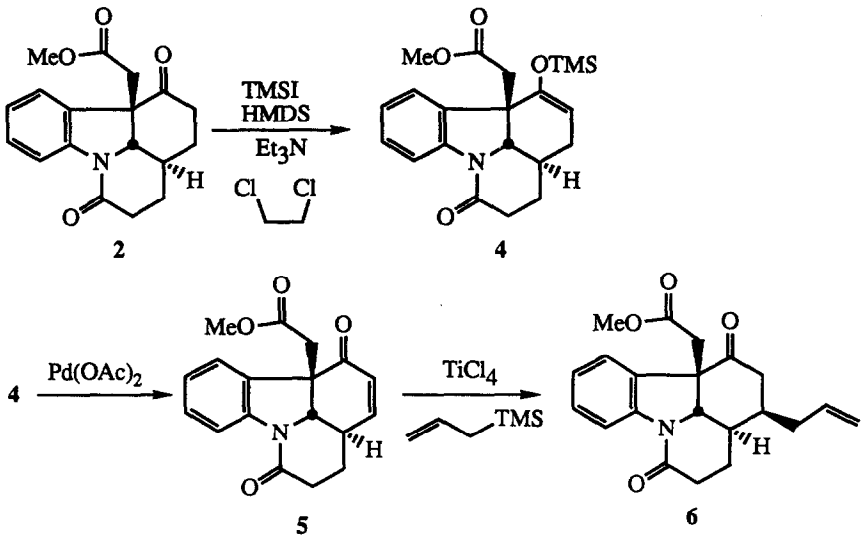


1



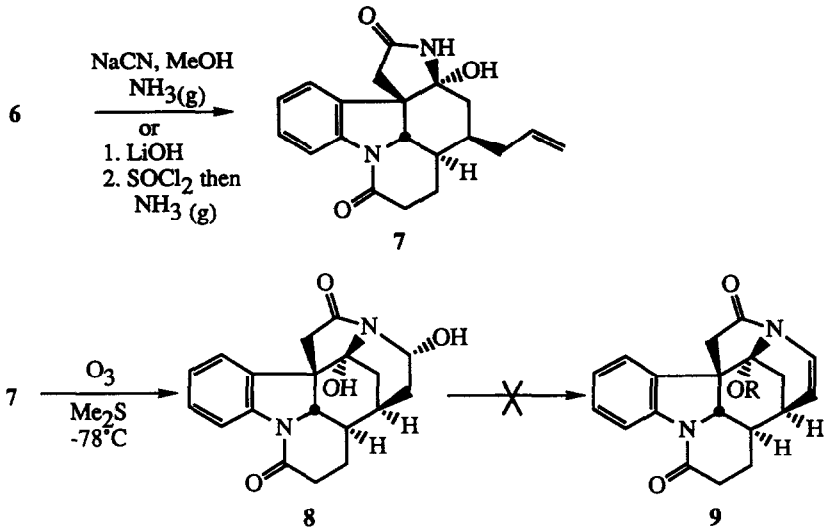
2: X=OMe **3**: X=H

Compounds **2** and **3** were advanced intermediates in our previously reported synthesis of a pentacyclic precursor. Generation of an unsaturated ketone in **2** had to be accomplished the presence of both an ester and an amide moiety. Although the reaction of **2** with TMSOTf and diisopropylethylamine returned starting material, the reaction with iodotrimethylsilane (TMSI), triethylamine and hexamethyldisilazane (HMDS) in 1,2-dichloroethane[6] furnished the desired enol silyl ether **4** in quantitative yield after

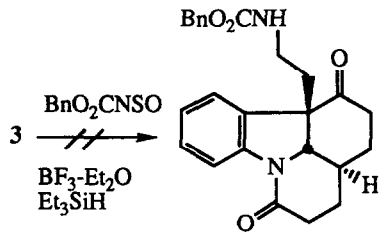


chromatography. Initial attempts to add a phenylselenenyl unit by the reaction of **4** with phenylselenenyl bromide produced an α-bromoketone. Phenylselenenyl halides have been shown to act as halogenating agents.[7] Elimination of this bromide was unsuccessful. The enol silyl ether **4** reacted with benzenesulfenyl chloride to produce a 1:1 mixture of sulfides which was oxidized to the sulfoxides. Thermolysis of the mixture of sulfoxides gave the unsaturated ketone **5**, but also returned 50% of the starting sulfoxide. Further investigation showed that the returned sulfoxide was only one diastereomer, the compound with the phenylsulfinyl moiety in the equatorial position. Attempts to force elimination of this equatorial sulfoxide failed. Fortunately, treatment of **4** with one equivalent of palladium acetate[8] in acetonitrile at 50°C for 48 h produced a 1:1 mixture of enone **5** and recovered enol silyl ether **4**. With the unsaturated ketone **5** in hand, the introduction of an allyl group was achieved by treatment of **5** with titanium tetrachloride and allyltrimethylsilane.[9] The main product that was produced was tentatively assigned structure **6**.

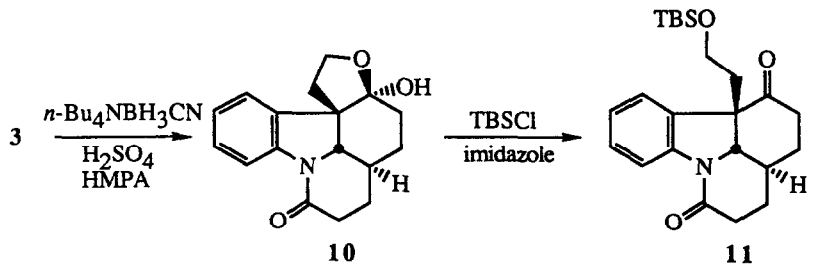
Reaction of keto ester **6** with sodium cyanide with ammonia[10] in a sealed tube produced the pentacyclic amide **7** in moderate yield. A sequence involving hydrolysis of the ester with lithium hydroxide, followed by treatment of the resulting acid with thionyl chloride in dichloromethane and addition of ammonia provided lactam **7** in better overall yield. Ozonolysis of the alkene afforded the hexacyclic lactam **8**. Attempts to convert lactam **8** to enamide **9** (MsCl, Et_3N; Ac_2O, DMAP; pTSA) led only to degradation of the starting material. The synthetic route to **8** suffered from low to moderate yields for certain steps and led to a lactam which could not be converted into a useful intermediate for the synthesis of strychnine. With these considerations in mind we turned to aldehyde **3**.



A most direct pathway for the selective functionalization of **3** would be the reductive carbamation[11] of **3**. Although this transformation was highly successful with simple aldehydes, our efforts to apply this

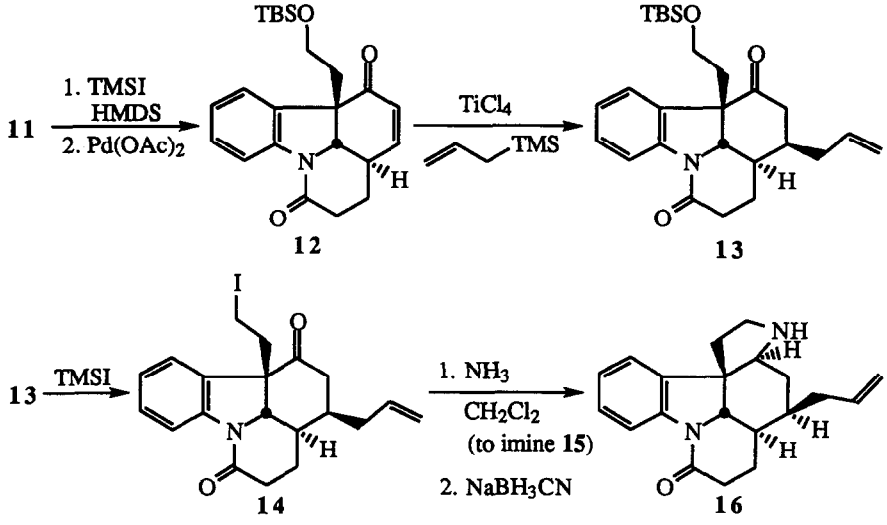


reaction to keto aldehyde **3** failed. Selective reduction of the aldehyde in the presence of the ketone was next attempted. Sodium borohydride and sodium triacetoxy borohydride[12] gave mixtures of the diol and the desired hemiketal. Selective reduction was finally realized with the combination of tetra-*n*-butylammonium cyanoborohydride and sulfuric acid in HMPA.[13] This gave the hemiketal **10** in excellent yield. Protection of the primary alcohol as a *tert*-butyldimethylsilyl ether[14] proceeded cleanly to provide the silyl ether **11**. Formation of the enol silyl ether followed by palladium acetate oxidation provided an inseparable mixture of the

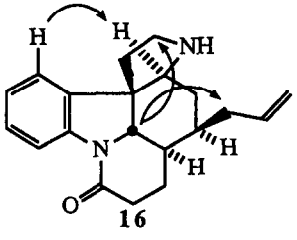


unsaturated ketone **12**.and ketone **11** in approximately a 1:1 ratio. The allyl group was installed using the Sakurai methodology to provide ketone **13** as the only isolated diastereomer.

With **13** in hand, we required a method to replace the ether with an amine. Oxidative deprotection of the TBDMS ether with trityl salts[15] afforded a hemiketal instead of the desired keto aldehyde. However, conversion of the silyl ether **13** to primary iodide **14** was successful with TMSI.[16] Dissolving this iodide in dichloromethane in a sealable tube, bubbling ammonia gas through the solution at -78 °C, and warming to ambient temperature provided an imine in excellent yield. Reduction of the imine with sodium cyanoborohydride gave the amine **16**.



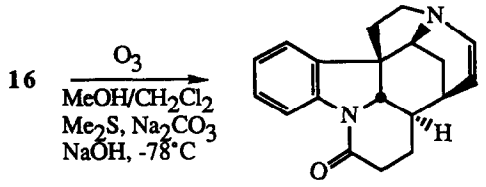
At this point it was possible to verify the stereochemistry of amine **16** by 2D NOESY experiments. The most important results of these experiments are the NOE interactions between the methine doublet at 3.71 ppm with the methylene of the allyl group, and with the methylene of the five-membered amine ring.



The lack of a NOE interaction between the methine doublet at 3.71 ppm and the methine proton at 3.63 ppm plus the presence of a NOE interaction between the proton on the aromatic ring and the methine proton at 3.63 ppm completed the assignment of stereochemistry of **16**.

Formation of the sixth ring was accomplished as shown below. Protection of the amine as the ammonium salt with trifluoroacetic acid during ozonolysis followed by workup under basic conditions gave the labile

bridgehead enamine **17** directly in approximately 40% isolated yield. The reaction of **17** with 9-BBN followed by oxidation afforded no recognizable products. Carbene addition reactions are currently being investigated.



17

The hexacyclic enamine **17** has been obtained in nine steps from aldehyde **3**. The route from **3** to **17** is superior to our earlier attempt from ester **2** in that the reactions exhibit better stereoselectivity and the conditions are more convenient. Intermediate **17** contains functional groups that we expect will be sufficient for the appendage of the final ring of strychnine.

Acknowledgement: We thank the Herman Frasch Foundation for partial support of this work. We thank the Lithium Division of the FMC Corporation for a generous gift of tert-butyldimethylchlorosilane.

EXPERIMENTAL

Unless noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes:ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (sgc). The purity of all title compounds was determined to be >95% by 300 MHz proton NMR and/or elemental analysis.

Methyl-6-(trimethylsilyloxy)-2,3,3a,4,6a,7a-hexahydropyrido- [3,2,1-jk]carbazole-6a-acetate (4): To a solution of the ketone **2** (0.58 g, 1.85 mmol) in 1,2-dichloroethane (10 mL) at 0°C were added hexamethyldisilazane (0.78 mL, 3.71 mmol) and triethylamine (0.52 mL, 3.71 mmol). After 5 min, iodotrimethylsilane (0.42 mL, 2.96 mmol) was added. This mixture was allowed to stir for 4 h at 0°C and then allowed to stir at rt overnight. The reaction mixture was recooled to 0°C, poured into ice-cold saturated $NaHCO_3$ and extracted with ether (3 x 10 mL). The organic extracts were washed once with ice-cold brine (15 mL), dried and concentrated. The resulting oil was then purified by sgc using 18 g of silica gel in a 30 mm column with a flow rate of 1:1 H:EA of 2.5 inches/min to yield 0.64 g (97%) of **4**: m.p. 100-101°C; R_f 0.44 (1:1 H:EA); ^1H NMR ($CDCl_3$) δ 8.13 (d, J=8.1 Hz, 1H), 7.58 (d, J=7.7 Hz, 1H), 7.24 (dt, J=7.8, 1.2 Hz, 1H), 7.03 (dt, J=7.3, 1.0 Hz, 1H), 4.94 (dd, J=6.9, 1.9 Hz, 1H), 4.35 (d, J=10.8 Hz, 1H), 3.58 (s, 3H), 2.91 (d, J=14.6 Hz, 1H), 2.65-2.75 (m, 1H), 2.55 (d, J=14.6 Hz, 1H), 2.45-2.55 (m, 1H), 2.16-2.19 (m, 1H), 1.90-2.15 (m, 2H), 1.50-1.70 (m, 2H), 0.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.5, 149.9, 140.1, 133.1, 128.3, 124.9, 123.3, 115.6, 102.1, 65.9, 51.1, 49.4, 44.2, 36.0, 31.2, 26.7, 24.2, -0.1, -0.1 (impurity); IR ($CDCl_3$) 2950, 1730, 1660, 1590, 1200, 870 cm^{-1}; HRMS m/z calc'd for $C_{21}H_{27}O_4Si$: 385.1709, found 385.1703; MS m/z 385, 312, 296, 256, 222, 149, 137.

Methyl-1,6-dioxo-2,3,3a,6,6a,7a-hexahydropyrido[3,2,1-jk]- carbazole-6a-acetate (5): To a solution of the enol silyl ether **4** (0.58g, 1.62 mmol) in acetonitrile (16 mL) was added $Pd(OAc)_2$ (0.40g, 1.79 mmol) as a solid. This was stirred for 48 h at 50°C. The resulting mixture was filtered through a pad of Celite, concentrated and purified by sgc using 2:3 H:EA to yield 0.24 g of **5** and 0.20 g of **4** which was recycled: m.p. 150-151°C; R_f 0.21 (2:3 H:EA); ^1H NMR ($CDCl_3$) δ 8.05 (d, J=8.3 Hz, 1H), 7.48 (dd, J=7.9, 1.2 Hz, 1H), 7.31 (dt, J=7.7, 1.3 Hz, 1H), 7.11 (dt, J=7.5, 1.0 Hz, 1H), 6.79 (dd, J=10.0, 1.9 Hz, 1H), 6.28 (dd, J=10.0, 3.0 Hz, 1H), 4.35 (d, J=9.5 Hz, 1H), 3.64 (s, 3H), 3.29 (d, J=17.1 Hz, 1H), 2.75-2.90 (m, 1H), 2.62 (d, J=17.1 Hz, 1H), 2.59 (dd, J=14.0, 1.0 Hz, 1H), 2.20-2.40 (m, 2H), 2.00 (dt, J=11.0, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5, 173.3, 170.8, 146.1, 141.0, 130.9, 129.6, 128.8, 124.7, 124.3, 116.23, 66.2, 53.5, 51.8, 45.3, 35.9, 31.5, 23.8; IR ($CDCl_3$) 1730, 1670, 1590, 1380, 1200 cm^{-1}; HRMS m/z calc'd for $C_{18}H_{17}O_4N$: 311.1158, found 311.1149; MS m/z 311, 256, 238, 222, 189, 168, 130.

Methyl-1,6-dioxo-4-(2-propenyl)-2,3,3a,4,5,6,6a,7a-octahydro- pyrido[3,2,1-jk]carbazole-6a-acetate (6): To a solution of the enone **5** (0.68 g, 2.19 mmol) in CH_2Cl_2 (35 mL) at -78°C, was added $TiCl_4$ (0.48 mL, 4.37 mmol). This was stirred 5 min and allyltrimethylsilane (0.87 mL, 5.47 mmol) was added. This mixture was stirred at -78°C for 2 h. The -78°C bath was removed and replaced with an ice bath. The mixture was allowed to stir at 0°C for 2 h, recooled to -78°C and 30 mL of water was added. The mixture allowed to warm to rt. The mixture was diluted with CH_2Cl_2 and separated. The organic layer was washed with brine, dried, concentrated and purified by sgc using 3:2 H:EAto yield 0.49 g of **6** and 0.24 g **5** (98% based on recovered starting material): m.p. 170-171°C; R_f 0.29 (3:2 H:EA); ^1H NMR ($CDCl_3$) δ 8.10 (d, J=7.9 Hz, 1H), 7.25-7.35 (m, 2H), 7.06 (d, J=4.1 Hz, 1H), 5.65-5.85 (m, 1H), 5.09-5.16 (m, 2H), 4.40 (d, J=10.5 Hz, 1H), 3.63 (s, 3H), 3.08 (d, J=16.6 Hz, 1H), 2.67-2.80 (m, 2H), 2.50-2.62 (m, 1H), 2.47 (d, J=16.6 Hz, 1H), 2.35-2.50 (m, 3H), 2.05-2.15 (m, 2H), 1.87-2.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 173.3, 170.9, 140.7, 135.9, 130.5, 129.5, 124.1, 122.7, 117.2, 116.3, 66.1, 56.9, 51.6, 43.0, 42.1, 41.3, 34.8, 31.6, 31.0, 21.5; IR ($CDCl_3$) 1735, 1705, 1675, 1590, 1470, 1460, 1380, 1200 cm^{-1}; HRMS m/z calc'd for $C_{21}H_{23}NO_4$: 353.16271, found 353.16226; MS m/z 353, 280, 256, 198, 184, 130; Analysis calc'd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; found: C, 71.14; H, 6.75.

12-(2-Propenyl)-13a-hydroxy-2,9-dioxo-1,2,3,10,11,11a,11b,12, 13,13a-decahydro-9*H*-pyrido[1,2,3-lm]pyrrolo{2,3-d]carbazole (7): To a solution of the ester **6** (0.21 g, 0.59 mmol) in MeOH: THF: H_2O (3.6: 3.6: 1) was added lithium hydroxide (0.027 g, 0.65 mmol) as a solid. This mixture was allowed to stir for 4 h at room temperature. The solvent was removed in vacuo and the residue was taken up in 2M HCl (10 mL) and methylene chloride (10 mL). The layers were separated and the aqueous layer was extracted with methylene chloride (5 x 10 mL). The organic layers were combined, dried and concentrated. This residue was taken up in 10 mL of methylene chloride. To this solution was added thionyl chloride (0.77 mL, 1.15 mmol). This mixture was heated at reflux for 4 h. The solvent was removed in vacuo and benzene was added and removed in vacuo. The residue was dissolved in methylene chloride and transferred to a dry sealable tube. The tube was cooled to -78°C and gaseous NH_3 was bubbled through the solution until the volume had doubled. The tube was sealed and allowed to stand overnight at rt. The tube was cooled to -78°C and opened. This was allowed to slowly warm to rt. After standing at room temperature for 1 h, nitrogen was

bubbled through the solution for 5 min. The solution was then diluted with methylene chloride and brine. The layers were separated and the aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined extracts were dried and concentrated. Purification by sgc using 1:3 H:EA gave 0.18 g (85% yield) of **7**: R_f 0.11 (1:3 H:EA); ^{1}H NMR ($CDCl_3$) δ 8.21 (d, J=8.0 Hz, 1H), 7.44 (d, J=7.5 Hz, 1H), 7.31 (t, J=7.8 Hz, 1H), 7.07 (d, J=7.5 Hz, 1H), 6.28 (br s, 1H), 5.15-5.33 (m, 1H), 5.06-5.18 (m, 2H), 3.97 (d, J=12.0 Hz, 1H), 2.73 (d, J=16.7 Hz, 1H), 2.59 (d, J=16.5 Hz, 1H), 2.32-2.60 (m, 3H), 1.70-2.30 (m, 7H); MS (CI (NH_3)) m/z 338 (M+1+NH_3-H_2O), 321 (M+1-H_2O), 298 (M+1-41), 279 (M-H_2O-41).

2,9-Dioxo-13a,15-dihydroxy-2,3,10,11,11a,11b,13,13a,14,15- decahydro-12*H*-1,12-ethano-9*H*-pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole (8): Ozone was bubbled through a solution of the olefin **7** (0.18 g, 0.53 mmol) in CH_2Cl_2 (15 mL) at -78°C until the solution turned light blue. Nitrogen was then bubbled through the solution until the solution cleared and dimethylsulfide (0.043 mL, 0.59 mmol) was added. The cold bath was removed and the reaction mixture was allowed to warm to rt. The solvent was removed and the residue was purified by sgc using EA to yield 0.12 g (67% yield) of **8**: R_f 0.14 (EA); ^{1}H NMR ($CDCl_3$) δ 8.09 (d, J=7.6 Hz, 1H), 7.76 (dd, J=1.4, 7.9 Hz, 1H), 7.30 (dt, J=1.4, 7.8 Hz, 1H), 7.10 (dt, J=1.0, 7.6 Hz, 1H), 5.83 (d, J=6.1 Hz, 1H), 3.26 (d, J=10.3 Hz, 1H), 3.16 (d, J=16.0 Hz, 1H), 2.77 (dd, J=3.8, 13.3 Hz, 1H), 2.50-2.68 (m, 3H), 2.39 (d, J=16.0 Hz, 1H), 2.22-2.32 (m, 2H), 1.92-2.08 (m, 2H), 1.75-1.90 (m, 2H); IR ($CDCl_3$) 3390 br, 1700, 1675, 1390 cm^{-1}; HRMS m/z calc'd for $C_{19}H_{20}N_2O_4$: 340.14231, found 340.14155; MS m/z 340, 322, 294, 279, 237, 222, 198, 130.

1,6-Dioxo-2,3,3a,4,5,6,6a,7a-octahydropyrido[3,2,1-jk]carbazole- 6a-ethanol (10): To a suspension of the aldehyde **3** (1.43 g, 5.01 mmol) in HMPA (17 mL) and concentrated H_2SO_4 (0.62 mL, 11.66 mmol) was added the n-Bu_4NBH_3CN as a solid. This was stirred 20 min, poured into water (40 mL) and extracted with ether (10 x 10 mL). Purification by sgc using 2:3 H:EA yielded 1.22 g (85%) of **10**: m.p. 197-198 °C; R_f 0.29 (2:3 H:EA); ^{1}H NMR ($CDCl_3$) δ 8.10 (d, J=7.5 Hz, 1H), 7.76 (d, J=7.3 Hz, 1H), 7.26 (dt, J=1.4, 7.8 Hz, 1H), 7.07 (dt, J=1.2, 7.6 Hz, 1H), 4.16 (dt, J=2.0, 7.9 Hz, 1H), 3.98 (q, J=8.4 Hz, 1H), 3.35 (d, J=10.0 Hz, 1H), 2.60-2.75 (m, 1H), 2.35-2.55 (m, 2H), 2.15-2.25 (m, 1H), 1.90-2.10 (m, 2H), 1.25-1.65 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 142.1, 131.2, 128.4, 125.9, 124.2, 115.7, 104.6, 68.2, 64.12, 55.5, 41.1, 38.4, 34.3, 31.6, 25.4, 25.1; IR ($CDCl_3$) 3600 br, 2940, 1675, 1475, 1390 cm^{-1}; HRMS m/z calc'd for $C_{17}H_{19}NO_3$: 285.13647, found 285.13649; MS m/z 285, 267, 226, 198, 184, 168, 156.

1,6-Dioxo-6a-(2-(*tert*-butyltrimethylsilyloxy)ethyl)-2,3,3a,4,5,6,6a, 7a-octahydropyrido[3,2,1-jk]carbazole (11): To a solution of the hemiketal **10** (4.42 g, 15.51 mmol) in DMF (30 mL) at rt were added imidazole (2.11 g, 31.02 mmol) and *tert*-butyldimethylsilyl chloride (TBSCl) (3.51 g, 23.26 mmol). The resulting mixture was allowed to stir overnight at rt, poured into water (60 mL) and extracted with ether (5 x 20 mL). The combined organic extracts were washed with brine, dried, concentrated and purified by sgc usnig 1:1 H:EA to yield 5.25g (85%) of **11**: m.p. 105°C; R_f 0.25 (1:1 H:EA); ^{1}H NMR ($CDCl_3$) δ 8.10 (dd, J=0.6, 7.8 Hz, 1H), 7.44 (dd, J=1.2, 7.6 Hz, 1H), 7.27 (dt, J=1.2, 7.7 Hz, 1H), 7.08 (dt, J=1.0, 7.5 Hz, 1H), 4.36 (d, J=10.5 Hz, 1H), 3.62 (t, J=5.9 Hz, 2H), 2.50-2.75 (m, 3H), 2.20-2.45 (m, 3H), 2.05-2.15 (m, 1H), 1.55-2.00 (m, 4H), 0.86 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.8, 169.9, 140.7, 130.8, 128.5, 125.2, 123.7, 115.6, 67.1, 59.4, 57.5, 43.8, 37.9, 31.1, 25.7, 25.3,

24.0, 18.0, -5.8, -5.9; IR (CH_2Cl_2) 2950, 1705, 1660, 1590, 1395 cm^{-1}; HRMS m/z calc'd for $C_{23}H_{33}NO_3Si$: 399.22297, found 399.22261; MS m/z 399, 342, 250, 240, 198, 186, 157, 127, 101, 75.

1,6-Dioxo-4-(2-propenyl)-6a-(2-(*tert*-butyltrimethylsilyloxy)ethyl- 2,3,3a,4,5,6,6a,7a-octahydropyrido[3,2,1-jk]carbazole (13): To a solution of the ketone **11** (1.05 g, 2.63 mmol) in 1,2-dichloroethane (20 mL) at 0°C were added hexamethyldisilazane (1.11 mL, 5.26 mmol) and triethylamine (0.73 mL, 5.26 mmol). This mixture was stirred 5 min and iodotrimethylsilane (0.60 mL, 4.21 mmol) was added. The resulting mixture was stirred at 0°C for 4 h and allowed to warm to rt overnight. The mixture was recooled to 0°C and poured into ice-cold saturated $NaHCO_3$. The layers were separated and the aqueous layer extracted with ether (2 x 20 mL). The combined organic extracts were washed once with ice-cold brine, dried, concentrated and the resulting oil purified by sgc using 3:1 H:EA, 18 g of silica gel in a 30 mm column with a flow rate of 2.5 in/min to yield 1.12 g (94%) of enol silyl ether: R_f 0.37 (3:1 H:EA); ^1H NMR ($CDCl_3$) δ 8.13 (d, J=8.0 Hz, 1H), 7.51 (d, J=7.7 Hz, 1H), 7.22 (dt, J=1.2, 7.8 Hz, 1H), 7.01 (dt, J=0.6, 7.4 Hz, 1H), 4.97 (dd, J=1.6, 7.0 Hz, 1H), 4.18 (d, J=10.7 Hz, 1H), 3.52-3.65 (m, 2H), 2.42-2.70 (m, 2H), 2.14 (ddd, J=16.0, 7.0, 3.8 Hz, 1H), 1.83-2.05 (m, 4H), 1.47-1.64 (m, 2H), 0.86 (s, 9H), 0.27 (s, 9H), -0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.0, 151.2, 140.5, 134.5, 127.8, 124.8, 123.3, 115.6, 101.8, 66.8, 59.9, 50.3, 43.4, 36.0, 31.3, 26.9, 25.7, 24.4, 24.4, 18.0, 0.1, 0.1, -5.6.

To a solution of the inseparable mixture of the saturated and unsaturated ketones (0.34 g) produced by palladium-mediated oxidation of the silyl enol ether of **11** (see prepartation of **4**) in CH_2Cl_2 (20 mL) at -78°C was added $TiCl_4$ (0.19 mL, 1.71 mmol). This mixture was stirred 5 min and allyltrimethylsilane (0.34 mL, 2.14 mmol) was added. Stirring was continued at -78°C for 2 h, The -78°C bath was replaced with a 0°C bath and stirring was continued for another 2 h. The mixture was then recooled to -78°C and the reaction was quenched by addition of 20 mL of water. The reaction mixture was diluted with CH_2Cl_2 and the layers were separated. The organic layer was washed once with brine, dried and concentrated. Purification by sgc using 7:3 H:EA yielded 0.16 g of the desired material as a single diastereomer and 0.12 g of **13**: m.p. 107°C; R_f 0.36 (3:1 H:EA); ^1H NMR ($CDCl_3$) δ 8.11 (d, J=8.0 Hz, 1H), 7.27 (dt, J=1.3, 7.8 Hz, 1H), 7.21 (dd, J=1.0, 7.4 Hz, 1H), 7.04 (dt, J=1.0, 7.4 Hz, 1H), 5.65-5.81 (m, 1H), 5.13 (d, J=9.2 Hz, 1H), 5.10 (dd, J=1.3, 15.9 Hz, 1H), 4.62 (d, J=10.6 Hz, 1H), 3.51-3.63 (m, 1H), 3.41-3.51 (m, 1H), 2.74 (dd, J=2.0, 17.4 Hz, 1H), 2.46-2.70 (m, 3H), 2.40 (ddd, J=1.4, 5.8, 17.5 Hz, 1H), 2.05-2.20 (m, 2H), 1.88-2.04 (m, 5H), 0.85 (s, 9H), -0.039 (s, 3H), -0.042 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 208.8, 171.4, 141.0, 135.5, 131.0, 129.1, 124.0, 117.5, 116.1, 64.8, 59.8, 58.3, 43.6, 42.7, 41.6, 34.2, 32.8, 31.7, 25.8, 21.9, 18.0, -5.6, -5.7; IR ($CDCl_3$) 2950, 2925, 1700, 1665, 835 cm^{-1}; HRMS m/z calc'd for $C_{26}H_{37}NO_3Si$: 439.25427, found 439.25419; MS m/z 439, 382, 352, 290, 262, 222, 197, 168, 131, 101, 75.

1,6-Dioxo-4-(2-propenyl)-6a-(2-iodoethyl)-2,3,3a,4,5,6,6a,7a-octa- hydropyrido[3,2,1-jk]carbazole (14): To a solution of the silyl ether **13** (0.35 g, 0.80 mmol) in CH_2Cl_2 (10 mL) at rt was added iodotrimethylsilane (0.12 mL, 0.84 mmol) with stirring. This mixture was allowed to stir for 1 h and poured into 10% $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic extracts were then washed with brine, dried and concentrated. The resulting oil was purified by sgc using 3:1 H:EA to yield 0.34 g (96%) of **14**: m.p. 201°C; R_f 0.34 (7:3 H:EA); ^1H NMR

($CDCl_3$) δ 8.11 (d, J=7.9 Hz, 1H), 7.31 (dt, J=1.2, 7.7 Hz, 1H), 7.22 (dd, J=1.0, 7.7 Hz, 1H), 7.08 (dt, J=1.0, 7.4 Hz, 1H), 5.79-5.64 (m, 1H), 5.15 (d, J=9.9 Hz, 1H), 5.11 (dd, J=1.1, 17.5 Hz, 1H), 4.00 (d, J=10.4 Hz, 1H), 2.96 (ddd, J=4.2, 8.8, 13.5 Hz, 1H), 2.48-2.82 (m, 6H), 2.40 (ddd, J=1.4, 5.4, 17.1 Hz, 1H), 2.32 (dt, J=4.6, 13.2 Hz, 1H), 2.05-2.15 (m, 1H), 1.91-2.05 (m, 3H), 1.67-1.80 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 207.3, 171.5, 141.1, 134.9, 129.7, 128.6, 124.3, 123.9, 118.0, 116.3, 65.6, 60.2, 45.2, 43.9, 41.6, 34.2, 33.0, 31.7, 21.6, -2.2; IR ($CDCl_3$) 2920, 1700, 1670, 1592, 1280, 1175 cm^{-1}; HRMS m/z calc'd for $C_{20}H_{22}NO_2I$: 435.06953, found 435.06977; MS m/z 435, 280, 266, 236, 222, 184.

12-(2-Propenyl)-9-oxo-2,3,10,11,11a,11b,12,13-octahydro-9*H*- pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole (15): Ammonia was bubbled through a solution of the iodide **14** (0.0634 g, 0.146 mmol) in CH_2Cl_2 (10 mL) at -78°C in a sealable tube for 5 min. The tube was sealed and allowed to stand at rt overnight. The tube was then cooled to -78°C and the tube opened. After the tube had warmed to rt for 1 h, nitrogen was bubbled through the solution for 5 min. The solution was diluted with methylene chloride and brine. The layers were separated and the aqueous layer was extracted with methylene chloride. The organic extracts were combined, dried and concentrated. The product was purified by sgc using EA to give 0.036 g (81% yield) of **15**: R_f 0.09 (EA); ^1H NMR ($CDCl_3$) δ 8.06 (d, J=7.9 Hz, 1H), 7.27 (dt, J=1.3, 7.8 Hz, 1H), 7.01 (dt, J=0.8, 7.5 Hz, 1H), 6.90 (dd, J=1.1, 7.0 Hz, 1H), 5.66-5.82 (m, 1H), 5.08 (d, J=10.5 Hz, 1H), 5.07 (dd, J=1.3, 17.2 Hz, 1H), 4.00 (dd, J=7.2, 15.5 Hz, 1H), 3.74-3.88 (m, 1H), 3.70 (d, J=10.8 Hz, 1H), 2.88 (dd, J=2.7, 14.2 Hz, 1H), 2.46-2.71 (m, 2H), 2.20-2.35 (m, 2H), 1.60-2.15 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 176.4, 173.2, 140.2, 135.4, 131.9, 129.1, 124.1, 122.2, 117.4, 116.6, 68.8, 60.1, 57.0, 43.3, 42.7, 35.7, 34.0, 31.7, 30.8, 21.5; IR (CH_2Cl_2) 1670, 1590, 1470, 1380 cm^{-1}.

9-Oxo-12-(2-propenyl)-1,2,3,10,11,11a,12,13,13a-decahydro-9*H*- pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole (16): To a solution of the imine **15** (0.0356 g, 0.116 mmol) in methanol (5 mL) with a trace of bromocresol green was added 2M HCl until the solution turned yellow. Sodium cyanoborohydride (5.1 mg, 0.081 mmol) was added as a solid and 2M HCl was added to just keep the solution yellow. This was stirred for 4 h. The solvent was removed and the residue taken up in 2M NaOH (15 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were dried, concentrated and purified by a silica gel prep plate using 3:2 H:EA to give 0.032 g (90% yield) of **16**: m.p. 123°C; R_f 0.096 (EA); ^1H NMR ($CDCl_3$) δ 8.12 (dd, J=1.4, 8.1 Hz, 1H), 7.27-7.19 (m, 2H), 7.06 (dt, J=1.1, 7.4 Hz, 1H), 5.91-5.76 (m, 1H), 5.11 (dt, J=1.0, 17.0 Hz, 1H), 5.10 (d, J=9.9 Hz, 1H), 3.71 (d, J=11.6 Hz, 1H), 3.63 (t, J=5.2 Hz, 1H), 3.22-3.02 (m, 2H), 2.70-2.44 (m, 2H), 2.44-2.32 (m, 1H), 2.31-2.17 (m, 1H), 2.13-1.57 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 171.9, 140.4, 137.5, 137.3, 127.9, 123.8, 122.2, 116.4, 115.7, 66.5, 59.7, 52.1, 45.1, 44.3, 39.7, 33.2, 33.0, 31.7, 21.5, 21.4; IR ($CDCl_3$) 3340 (br), 2930, 1660, 1592, 1395 cm^{-1}; HRMS m/z calc'd for $C_{20}H_{24}N_2O$: 308.18886, found 308.18890; MS m/z 308, 265, 251, 236, 223, 198, 168, 144, 130, 56.

9-Oxo-2,3,10,11,11a,11b,13,13a-octahydro-12*H*-1,12-ethano-9*H*- pyrido[1,2,3-lm]pyrrolo[2,3-d]carbazole (17): To a solution of the amine **16** (0.028 g, 0.092 mmol) in a mixture of CH_2Cl_2 and CH_3OH (5:1, 4.5 mL) was added trifluoroacetic acid (0.014 mL, 0.184 mmol). The resulting mixture was cooled to -78°C. Ozone was bubbled through the solution until the solution turned light blue. The ozone stream was replaced with a stream of N_2 and N_2 was bubbled through the solution for 5 min. Dimethyl

sulfide (3 drops), anhydrous Na_2CO_3 and 2M NaOH (2 drops) were added with stirring and the cold bath was removed. This mixture was allowed to warm to rt, filtered and concentrated. The crude material was purified using one inch of silica gel in a Pasteur pipette with 1:3 H:EA to give **17** (0.020g, 75% yield): R_f 0.44 (slow decomposition on silica gel) (1:3 H:EA); ^1H NMR ($CDCl_3$) δ 8.07 (d, J=8.1 Hz, 1H), 7.25 (dt, J=1.5, 7.6 Hz, 1H), 7.21 (dd, J=1.2, 7.0 Hz, 1H), 7.10 (dt, J=1.0, 7.4 Hz, 1H), 5.98 (d, J=7.7 Hz, 1H), 4.84 (dt, J=1.2, 6.8 Hz, 1H), 3.72 (br s, 1H), 3.45 (d, J=10.3 Hz, 1H), 3.36 (ddd, J=7.4, 10.0, 12.0 Hz, 1H), 3.16 (ddd, J=4.0, 8.9, 12.4 Hz, 1H), 2.66 (ddd, J=7.8, 11.1, 16.1 Hz, 1H), 2.49 (ddd, J=2.7, 8.2, 16.1 Hz, 1H), 2.32-2.22 (m, 2H), 2.17-2.10 (m, 1H), 1.91-1.70 (m, 4H), 1.49-1.36 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 173.2, 141.5, 139.9, 134.2, 128.3, 124.2, 121.9, 116.1, 102.2, 69.4, 59.3, 53.5, 51.5, 47.4, 46.4, 31.7, 28.4, 27.4, 22.5.

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