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# Novel heterocyclic systems. Synthesis of 2,7-dimethyl-10-oxa-1,8-diaza-anthracen-9-one and derivatives

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**Abstract**—Synthesis of novel heterocycles, which contain the unique 10-oxa-1,8-diazaanthracen-9-one tricyclic core, is reported. The core structure was assembled via a dehydrative-cyclization strategy.


## 1. Introduction

During a recent effort in our laboratories directed at the development of chiral ketones for use as asymmetric epoxidation catalysts,[1] we synthesized a series of heterocycles containing the novel 10-oxa-1,8-diazaanthracen-9-one backbone, i.e. compounds **1** and **2** (Fig. 1).

Compounds with related frameworks include 1,8-diaza-10-oxa-9-thia-9,10-dihydroanthracene (**3**)[2], 2,7-bis[2-(*N*,*N*-diethylamino)ethoxy]-1,8-diazafluorenone dihydrochloride (**4**) and tilorone (**5**) (Fig. 2).[3] Compounds such as **3** are of interest for their potential biological activity as central nervous system agents and can be synthetically obtained by the condensation of the disodium salt of 2-mercapto-3-hydroxypyridine and 2-chloro-3-nitropyridine.[2] The 1,8-diazafluorenone **4** is a weakly active interferon inducer in mice and shows interaction with calf thymus DNA similar to that of tilorone (**5**), which in turn exhibits antitumor, anti-inflamatory, immunostimulating, interferogenic and virucidal biological activities.[3] The first synthesis of dimethyl-10-oxa-1,8-diaza-anthracen-9-one (**1**) and the novel derivative **2** are reported herein.

## 2. Results and discussion

Our approach to ketone **1** involves the preparation and coupling of pyridines **6** and **7**. Formylation of the known iodide **6**[4] provided aldehyde **7** in 75% yield (Scheme 1).[5]

Nucleophilic addition to **7** by the organolithium species derived from iodide **6** via lithium–halogen exchange afforded alcohol **8**. Benzylic oxidation,[6] followed by methyl ether cleavage using aqueous hydrobromic acid yielded ketone **10**.[7]

Exposure of diol **10** to a solution of hydrobromic acid in refluxing acetic acid provided the desired ketone **1**. Alternatively, ketone **9** could be converted to tricycle **1** by direct exposure to refluxing hydrobromic acid in acetic acid, presumably via compound **10**. Mechanistically, diol **10** undergoes a dehydrative-cyclization to provide ketone **1** via intermediate **12** (Scheme 2).[8]

We also developed a mild, two-step protocol for the preparation of ketone **1** from **10** that avoided the use of the harsh HBr/acetic acid medium needed for the dehydrative-cyclization (Scheme 1). Triflation of both hydroxyls in **10** afforded the cyclization precursor **11**. The use of Pd(0) or Ni(0) catalysts did not result in carbon–carbon bond formation at the C-3 positions of the pyridine rings. Instead, the oxo-bridged compound **1** was formed as the sole product. This conversion is presumed to be the result of oxidative addition of the transition metal complex to one of the carbon-trifluoromethanesulfonate bonds. Aqueous hydrolysis of the other trifluoromethanesulfonate moiety promoted by the transition metal complex present, followed by a dehydrating cyclization similar to that operating in Scheme 2, gave the unanticipated product **1**.

Recrystallization from $CHCl_3$/hexanes (1:1) yielded X-ray quality crystals of ketone **1**, which on X-ray analysis unambiguously confirmed the novel 10-oxa-1,8-diaza-anthracen-9-one atom connectivity present in ketone **1** (Fig. 3).[9]

*Keywords*: Heterocycle; 10-Oxa-1,8-diaza-anthracen-9-one; Dehydrative cyclization.
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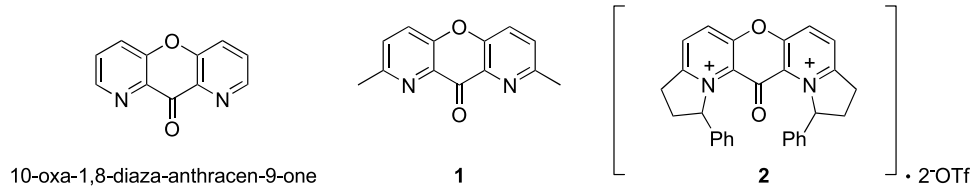



**Figure 1.** Novel heterocyclic compounds containing the 10-oxa-1,8-diazaanthracen-9-one backbone.

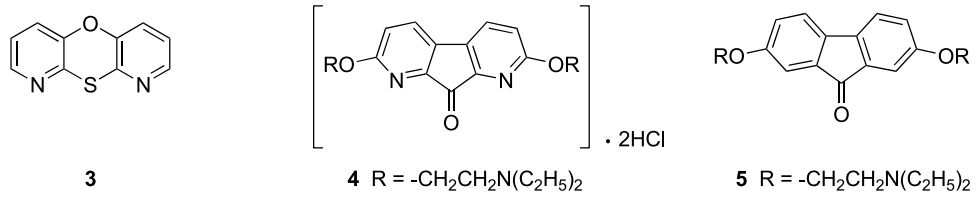
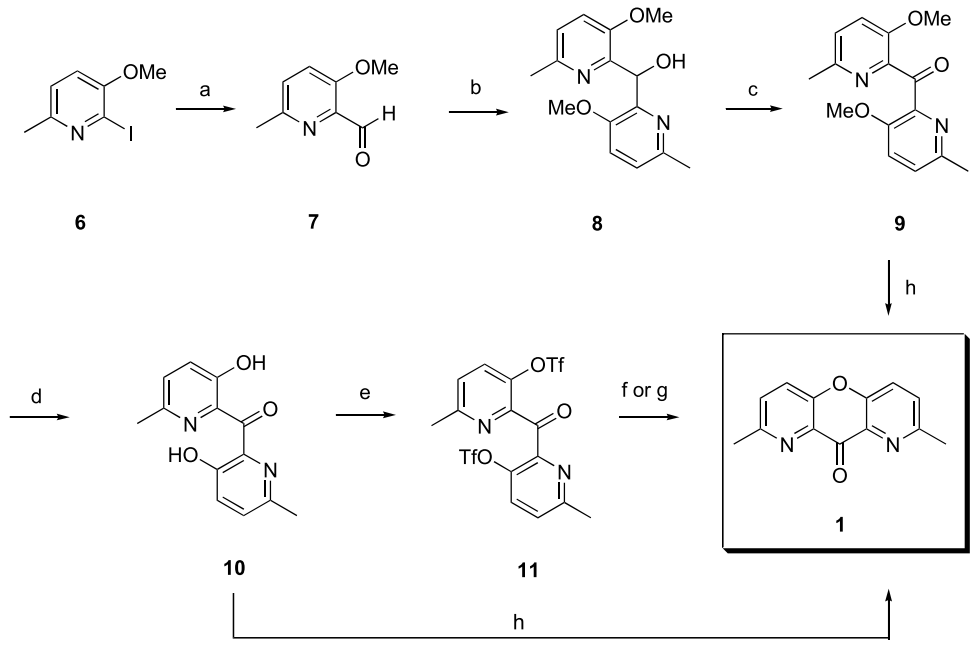
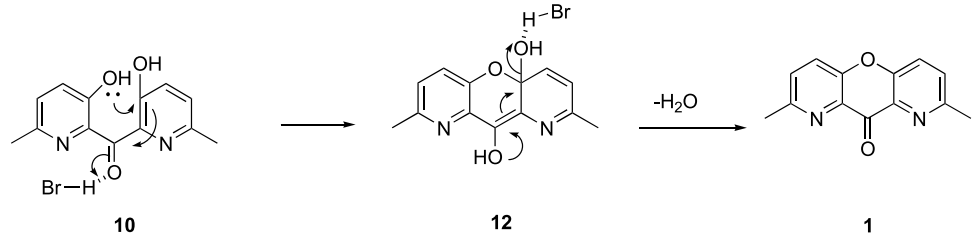



**Figure 2.** Biologically active heterocycles with related frameworks to that of 10-oxa-1,8-diaza-anthracene-9-one.




**Scheme 1.** (a) *n*-BuLi, DMF (75%); (b) *n*-BuLi/**6**, then **7** (59%); (c) $MnO_2$, $CH_2Cl_2$ (100%); (d) HBr (48% solution in $H_2O$) (92%); (e) $Tf_2O$, pyridine, $CH_2Cl_2$ (96%); (f) $(Ni(COD)_2)$, DMF, 60 °C (83%); (g) $PdCl_2$, bis(pinacolato)diboron, 80 °C; then $PdCl_2$, $Na_2CO_3$ (2 M solution in $H_2O$) (55%); (h) HBr (30% solution in AcOH), reflux (99%).




**Scheme 2.**

Efforts to produce **2** directly from ketone **1** via lateral metalation/alkylation were unsuccessful. Attempts to deprotonate and subsequently alkylate the lateral methyl groups in anthracenone **1** with styrene oxide failed. The use of LiHMDS or KHMDS in THF or a 1:1 mixture of THF and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU) at various reaction temperatures did not result in the formation of the desired dianion. This result prompted us

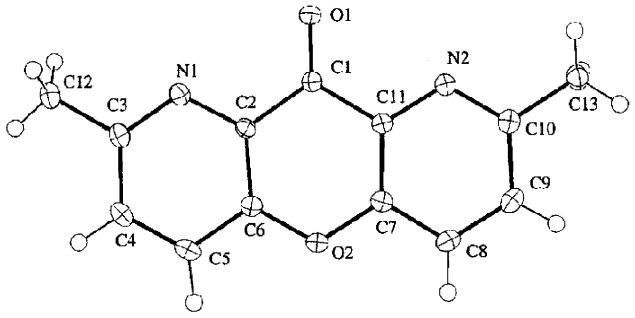
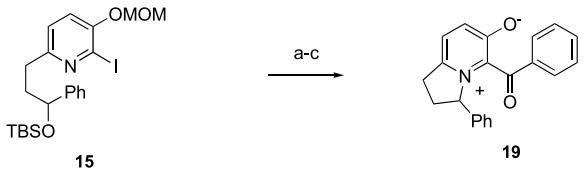



**Figure 3.** Crystal structure of tricyclic ketone **1**.

to explore alkylation conditions with the 1,3-dioxolane protected ketone. Attempted deprotonation of the lateral methyl groups of the cyclic ketal under a variety of basic conditions quantitatively returned the starting material or resulted in competitive deprotonation of the pyridine rings. We next turned our attention to installing the phenylethyl side chain first. Generation of the dianion from commercially available pyridinol **13** using *sec*-BuLi, and subsequent nucleophilic addition to styrene oxide followed by regiospecific iodination at C-2, generated diol **14** (Scheme 3).[10] Disilylation with TBSCl, followed by selective hydrolysis of the aromatic TBS ether[11] and protection of the resulting pyridinol as the methoxymethyl ether, yielded iodide **15** in good yield.[12] Formylation of the lithiated species resulting from lithium-halogen exchange on **15** was achieved by trapping with ethyl formate rather than dimethylformamide, as the latter gave lower yields of the desired aldehyde **16**. Nucleophilic addition to compound **16** by the aryllithium generated from iodide **15** and *n*-BuLi afforded alcohol **17**. Benzylic oxidation with $MnO_2$ was followed by selective deprotection of the MOM group with dimethylboron bromide in the presence of the TBS ether.[13] Subsequent triflation of the resulting diol yielded bis-trifluoromethane sulfonate **18**. Similar to the synthesis of **1**, exposure of **18** to bis(1,5-cyclooctadiene)nickel(0) ($Ni(COD)_2$) resulted in the formation of the 10-oxa-1,8,-diaza-anthracene-9-one backbone. Removal of the TBS ether, triflation and in situ cyclization yielded the targeted polyheterocyclic ketone **2** as a mixture of diastereomers.

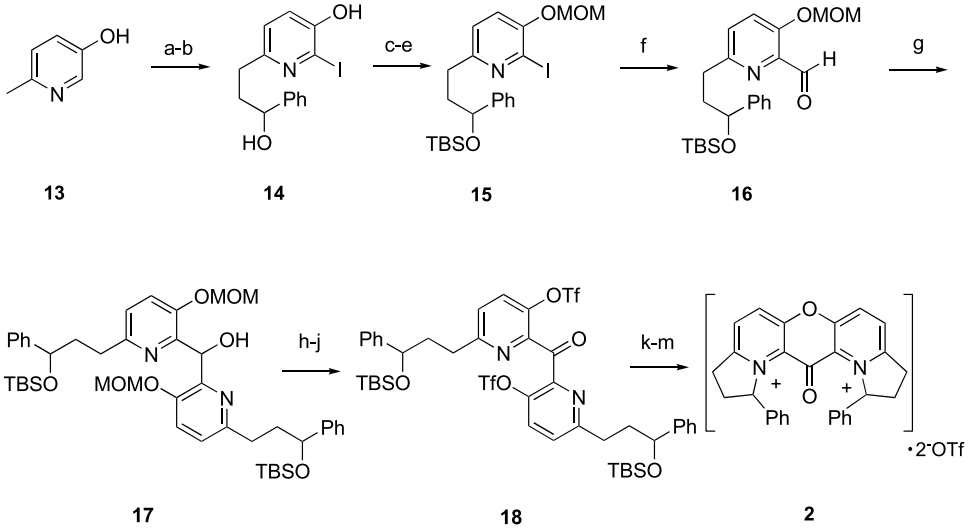
The cylcization of tethered benzylic triflates to provide highly substituted indolizidinium compounds has been extended to the formation of compound **19**. Using similar methodology for the synthesis of ketone **2**, acylation of the methoxymethyl-protected pyridinol **15** using *n*-BuLi and benzoyl chloride, followed by TBS-deprotection, triflation and in situ cyclization yielded the novel racemic zwitterion **19**. Interestingly, the methoxy methyl group proved to be labile upon formation of the indolizidinium ring, and compound **19** was isolated rather than its MOM-protected analog (Scheme 4).




**Scheme 4.** (a) *n*-BuLi, PhCOCl (69%); (b) TBAF, THF (80%); (c) $Tf_2O$, DIEA, $CH_2Cl_2$ (67%).

## 3. Conclusions

In summary, the synthesis of the novel heterocycles **1** and **2** was accomplished from commercially available materials in 6 and 13 steps, respectively. A novel transition metal-catalyzed dehydrating cyclization was discovered which circumvented the use of a strongly acidic reaction medium to afford the tricyclic core. The unprecedented 10-oxa-1,8-diazaanthracen-9-one backbone of **1** and **2** was unambiguously determined by X-ray crystallographic analysis. Similar to the synthesis of compound **2**, the cyclization of tethered benzylic triflates can be expected to generate other highly substituted indolizidinium compounds. Although this study used racemic styrene oxide, the methodology could




**Scheme 3.** (a) *sec*-BuLi, then styrene oxide (64%); (b) $Na_2CO_3$, $I_2$, THF/$H_2O$ 1:1 (63%); (c) TBSCl, imidazole, DMF (91%); (d) AcOH/THF/$H_2O$ 4:2:1 (77%); (e) MOMCl, DIEA, THF (92%); (f) *n*-BuLi, ethyl formate (75%); (g) *n*-BuLi/**15**, then **16** (68%); (h) $MnO_2$, $CH_2Cl_2$ (100%); (i) $Me_2BBr$, $CH_2Cl_2$ (88%); (j) $Tf_2O$, pyridine (97%); (k) $Ni(COD)_2$, DMF (66%); (l) TBAF, THF (83%); (m) $Tf_2O$, DIEA, $CH_2Cl_2$ (99%).

lead to enantiopure ketones by alkylating the dianion of 5-hydroxy-2-methylpyridine with the corresponding optically active epoxide, either antipode of which being commercially available.

## 4. Experimental

### 4.1. General procedures

All reactions were performed in oven or flame dried glassware under argon atmosphere and stirred magnetically. Tetrahydrofuran (THF) and toluene were distilled from sodium/benzophenone ketyl prior to use. Trifluoromethanesulfonic anhydride (triflic anhydride) was distilled and stored under argon. Other reagents and solvents from commercial sources were stored under argon and used directly. Melting points were obtained from a Thomas-Hoover capillary melting point apparatus and are uncorrected. Radial preparative layer chromatography (radial PLC) was performed on a Chromatotron (Harrison Associates, Palo Alto, CA) using glass plates coated with 1, 2 or 4 mm layers of Kieselgel 60 PF254 containing gypsum. High-resolution mass spectral analysis (HRMS) was performed at North Carolina State University. Elemental analyses were performed by Atlantic Microlab Inc. NMR spectra were obtained using a Varian Gemini GN-300 (300 MHz), Varian Mercury 300 (300 MHz), or Varian Mercury 400 (400 MHz) spectrometer. Chemical shifts are in $\delta$ units (ppm) with TMS (0.0 ppm) used as the internal standard for $^1$H NMR spectra and the $CDCl_3$ absorption (77.2 ppm) or $C_6D_6$ absorption (128.4 ppm) for $^{13}$C NMR spectra. IR spectra were recorded on a Perkin–Elmer 1430 spectrometer. HPLC was performed using Waters and Associates (Milifrod, MA) 600 E multi solvent delivery system with a 486 tunable detector equipped with an YMC-pack sil (150×4.6 mm I.D.) analytical column or an YMC-pack sil (150×10 mm I.D.) preparative column.

**4.1.1. Bis-(3-methoxy-6-methylpyridin-2-yl)methanol (8).** To a stirred solution of compound **6** (138 mg, 0.550 mmol) in THF (3 mL) at −78 °C was added *n*-BuLi (2.40 M in hexanes, 250 μl, 0.605 mmol) dropwise over 5 min. The resulting solution was stirred for additional 15 min and then compound **7** (91.0 mg, 0.605 mmol) in THF (2.0 mL) was added over 10 min. The mixture was strirred at −78 °C for 2 h and then warmed gradually to 0 °C over 1 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (30 mL), and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and the solvent was removed in vacuo. Purification by silica gel chromatography (20 to 30% EtOAc in hexanes) gave 89.0 mg (59%) of the desired product **8** as a white solid: mp 116.0–117.5 °C; IR (neat) 3425, 1639, 1464, 1253 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.03 (m, 4H), 6.23 (bs, 1H), 6.00 (bs, 1H), 3.65 (s, 6H), 2.45 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 151.4, 149.3, 148.5, 122.5, 118.9, 67.4, 56.0, 23.5. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.79; H, 6.60; N, 10.29.

**4.1.2. Bis-(3-methoxy-6-methylpyridin-2-yl)methanone (9).** To a solution of **8** (2.94 g, 10.7 mmol) in anhydrous $CH_2Cl_2$ (100 mL) was added activated $MnO_2$ (13.96 g, 160.7 mmol), and the resulting mixture was stirred at rt for 48 h under an argon atmosphere. The manganese residues were removed by filtration through Celite, and then washed with $CH_2Cl_2$ (500 mL). The filtrate was evaporated in vacuo. Purification by silica gel chromatography (80 to 100% EtOAc in hexanes) gave 2.92 g (100%) of the desired product **9** as a white solid: mp 147–148 °C; IR (neat) 2928, 1676, 1464, 1263 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.21 (d, $J$=8.6 Hz, 2H), 7.17 (d, $J$=8.6 Hz, 2H), 3.68 (s, 6H), 2.45 (s, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 193.2, 153.2, 149.5, 145.2, 126.0, 120.3, 56.1, 23.4. Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.02; H, 6.02; N, 10.22.

**4.1.3. Bis-(3-hydroxy-6-methylpyridin-2-yl)methanone (10).** Compound **9** (530 mg, 1.95 mmol) was dissolved in aqueous HBr (48% in $H_2O$, 30 mL, 0.265 mol). The reaction mixture was refluxed for 24 h, cooled to rt, and the mixture was concentrated in vacuo. To the residue was added aqueous saturated $NaHCO_3$ (50 mL), and the mixture was extracted with EtOAc (3×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (30 to 50% EtOAc in hexanes) gave 438 mg (92%) of the desired product **10** as a yellow solid: mp 157–158 °C; IR (neat) 3000, 1618, 1582, 1468, 1311 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 14.15 (s, 2H), 7.47 (d, $J$=8.6 Hz, 2H), 7.38 (d, $J$=8.6 Hz, 2H), 2.61 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 195.1, 157.0, 149.0, 136.3, 130.7, 130.4, 23.2. Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.90; H, 5.02; N, 11.50.

**4.1.4. Trifluoromethanesulfonic acid 6-methyl-2-(6-methyl-3-trifluoromethanesulfonyloxy-pyridine-2-carbonyl)pyridin-3-yl ester (11).** A solution of **10** (121 mg, 0.495 mmol) and pyridine (400 μl, 4.96 mmol) in anhydrous $CH_2Cl_2$ (5 mL) was cooled to 0 °C under argon. A solution of freshly distilled triflic anhydride (330 μl, 1.98 mmol) in $CH_2Cl_2$ (1.0 mL) was added dropwise over a period of 5 min. The contents of the flask were allowed to warm to rt over 30 min and then stirred for 3 h. The reaction mixture was filtered through Celite with $CH_2Cl_2$, and the solvent was removed in vacuo. Purification by silica gel chromatography (10 to 20% EtOAc in hexanes) gave 243 mg (96%) of the desired product **11** as a white solid: mp 82.5–83.5 °C; IR (neat) 2921, 1702, 1584, 1430, 1307, 1215 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.63 (d, $J$=8.6 Hz, 2H), 7.42 (d, $J$=8.6 Hz, 2H), 2.54 (s, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 188.8, 158.8, 145.9, 143.8, 130.4, 127.8, 118.6 (1C, q, $J$=317.5 Hz), 23.9; $^{19}$F NMR ($CDCl_3$, 300 MHz) $\delta$ 74.0. Anal. Calcd for $C_{15}H_{10}F_6N_2O_7S_2$: C, 35.44; H, 1.98; N, 5.51. Found: C, 35.43; H, 1.98; N, 5.50.

**4.1.5. 2,7-Dimethyl-10-oxa-1,8-diazaanthracen-9-one (1).** *Method A*. To a solution of **11** (1.038 g, 2.040 mmol) in anhydrous DMF (30 mL) at rt was added $Ni(COD)_2$ (618 mg, 2.25 mmol). The resulting mixture was heated at 60 °C for 72 h. Saturated aqueous $NaHCO_3$ (150 mL) was added, and the reaction mixture was extracted with $CH_2Cl_2$ (3×150 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (20 to 30%

EtOAc in hexanes) gave 357 mg (83%) of the desired product **1** as a yellow solid: mp 255–257 °C; IR (neat) 3037, 1672, 1467, 1274 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.79 (d, $J=8.4$ Hz, 2H), 7.53 (d, $J=8.4$ Hz, 2H), 2.76 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 175.3, 157.0, 151.8, 137.8, 129.5, 127.3, 24.6; HRMS $(M+H)^+$ calcd for $C_{13}H_{10}N_2O_2$ 227.0821, found 227.0817.

*Method B*. A flask charged with **11** (400 mg, 0.787 mmol), bis(pinacolato)diboron (100 mg, 0.393 mmol) and $PdCl_2$ (58 mg, 0.079 mmol) was flushed with argon. DMF (12 mL) was added, the reaction mixture degassed, and the contents of the flask heated at 80 °C for 2 h. The solution was cooled to rt and $PdCl_2$ (58 mg, 0.079 mmol) and $Na_2CO_3$ (2.0 M in $H_2O$, 1.0 mL, 2.0 mmol) were added. The reaction mixture was heated at 80 °C for 24 h. The mixture was cooled to rt and filtered through Celite with MeOH (30 mL). The filtrate was washed with $H_2O$ (30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel chromatography (20 to 30% EtOAc in hexanes) gave 91.0 mg (55%) of the desired product **1** as a yellow solid.

*Method C*. Compound **10** (421 mg, 1.55 mmol) was dissolved in HBr (30% in AcOH, 20 mL, 0.10 mol). The reaction mixture was refluxed for 48 h, cooled to rt, and concentrated in vacuo. To the residue was added aqueous saturated $NaHCO_3$ (50 mL), and the mixture was extracted with EtOAc (3×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (20 to 30% EtOAc in hexanes) gave 346 mg (99%) of the desired product **1** as a yellow solid.

**4.1.6. 6-(3-Hydroxy-3-phenylpropyl)-2-iodopyridin-3-ol (14).** A solution of 5-hydroxy-2-methylpyridine (**13**) (1.25 g, 11.5 mmol) in THF (80 mL) was cooled to −20 °C. A solution of *sec*-BuLi (0.97 M in cyclohexane, 24.1 mL, 24.1 mmol) was added dropwise over a period of 5 min. The resulting dark red mixture was stirred at −20 °C for an additional 45 min. The mixture was cooled to −78 °C and neat styrene oxide (6.5 mL, 57 mmol) was added over a period of 10 min. After 2 h, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ (100 mL) and warmed up to rt, during which time it became colorless. The mixture was extracted with $CH_2Cl_2$ (3×100 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (50 to 100% EtOAc in hexanes) gave 1.68 g (64%) of the desired diol product as a colorless oil; IR (neat) 3027, 2360, 1574, 1494, 1452, 1275, 1124, 1060, 911 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 8.14 (s, 1H), 7.93 (bs, 1H), 7.33 (bs, 1H), 7.22 (m, 5H), 7.11 (d, $J=2.3$ Hz, 1H), 7.00 (d, $J=8.5$ Hz, 1H), 4.80 (t, $J=5.8$ Hz, 1H), 2.87 (t, $J=6.7$ Hz, 2H), 2.12 (q, $J=6.3$ Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 153.0, 151.5, 144.6, 135.6, 128.5, 127.4, 126.0, 125.8, 124.6, 74.1, 38.4, 33.1; HRMS $(M+H)^+$ calcd for $C_{14}H_{15}NO_2$ 230.1181, found 230.1193.

To a solution of the above diol (1.68 g, 7.33 mmol) and $Na_2CO_3$ (1.63 g, 15.4 mmol) in 1:1 $H_2O$/THF (220 mL) was added $I_2$ (1.86 g, 7.33 mmol). After stirring at rt for 1 h, the iodine color disappeared and the reaction was quenched with 10% HCl dropwise until the solution pH was 3. The mixture was filtered through Celite, and the solvent removed in vacuo. Purification by silica gel chromatography (50 to 100% EtOAc in hexanes) gave 1.63 g (63%) of the desired product **14** as a white foam; IR (neat) 3060, 2342, 1557, 1454, 1288, 1064, 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.30 (m, 5H), 7.09 (d, $J=8.1$ Hz, 1H), 6.96 (d, $J=8.1$ Hz, 1H), 6.10 (bs, 1H), 4.78 (t, $J=6.3$ Hz, 1H), 3.75 (bs, 1H), 2.84 (m, 2H), 2.13 (q, $J=6.8$ Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 155.6, 151.0, 144.7, 128.6, 127.6, 126.1, 123.8, 122.5, 110.0, 74.1, 38.5, 33.3; HRMS $(M+H)^+$ calcd for $C_{14}H_{14}INO_2$ 356.0148, found 356.0140.

**4.1.7. 6-[3-(*tert*-Butyldimethylsilanyloxy)-3-phenylpropyl]-2-iodo-3-methoxymethoxypyridine (15).** To a solution of **14** (1.07 g, 3.01 mmol) in DMF (30 mL) at 20 °C was added imidazole (1.64 g, 24.1 mmol) and *tert*-butyldimethylsilyl chloride (1.81 g, 12.0 mmol). The resulting mixture was stirred at rt for 12 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL) and extracted with $CH_2Cl_2$ (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over $Na_2SO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (0 to 10% EtOAc in hexanes) gave 1.60 g (91%) of the desired bissilyl ether product as a colorless oil; IR (neat) 2953, 2855, 1541, 1441, 1361, 1295, 1255, 1091, 1059, 896, 836, 776 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.63 (m, 7H), 5.10 (t, $J=5.6$ Hz, 1H), 3.12 (m, 2H), 2.41 (m, 2H), 1.43 (s, 9H), 1.26 (s, 9H), 0.64 (s, 6H), 0.39 (s, 3H), 0.22 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 156.4, 150.6, 145.5, 128.3, 127.2, 126.3, 126.2, 124.8, 122.3, 115.3, 74.8, 40.9, 33.4, 26.1, 26.0, 18.5, −3.8, −3.8, −4.4, −4.7; HRMS $(M+H)^+$ calcd for $C_{26}H_{42}INO_2Si_2$ 584.1877, found 584.1879.

The above bissilyl ether (1.60 g, 2.74 mmol) was dissolved in a 4:2:1 mixture of $CH_3COOH/H_2O$/THF (250 mL) at 20 °C and stirred for 4 h. The reaction mixture was carefully quenched with saturated aqueous $NaHCO_3$ (300 mL) and extracted with $CH_2Cl_2$ (3×300 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (10 to 30% EtOAc in hexanes) gave 995 mg (77%) of the desired product as a white foam; IR (neat) 3418, 2956, 2856, 1545, 1488, 1359, 1286, 1248, 1085, 981 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.29 (m, 5H), 7.09 (d, $J=8.0$ Hz, 1H), 6.94 (d, $J=8.1$ Hz, 1H), 5.30 (bs, 1H), 4.72 (t, $J=5.4$ Hz, 1H), 2.74 (m, 2H), 2.04 (m, 2H), 0.89 (s, 9H), 0.02 (s, 3H), −0.16 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 156.1, 151.1, 145.3, 128.3, 127.2, 126.0, 126.4, 122.4, 110.2, 74.7, 41.1, 33.1, 26.1, 18.4, −4.4, −4.7; HRMS $(M+H)^+$ calcd for $C_{20}H_{28}INO_2Si$ 470.1012, found 470.1027.

A solution of the above phenol (1.29 g, 2.75 mmol) in THF (65 mL) was cooled to 0 °C and *N*,*N*-diisopropylethylamine (1.0 mL, 5.43 mmol) was added dropwise over a period of 5 min. After stirring at 0 °C for 15 min, chloromethyl methyl ether (1.50 mL, 19.0 mmol) was added dropwise over 5 min. The mixture was stirred for 30 min, then gradually warmed to rt. After stirring at 20 °C for 40 h, the reaction mixture was quenched with a buffered solution (pH 8) of $NH_4OH$ and $NH_4Cl$ (275 mL) and then extracted

with ethyl acetate (3×250 mL). The combined organic layers were dried over $MgSO_4$, filtered through Celite with ethyl acetate, and concentrated in vacuo. Purification by silica gel chromatography (0 to 10% EtOAc in hexanes) gave 1.30 g (92%) of **15** as a colorless oil; IR (neat) 2958, 1551, 1488, 1291, 1246 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.29 (m, 5H), 7.15 (d, $J$=8.4 Hz, 1H), 6.96 (d, $J$=8.4 Hz, 1H), 5.21 (s, 2H), 4.74 (t, $J$=5.4 Hz, 1H), 3.50 (s, 3H), 2.77 (m, 2H), 2.06 (m, 2H), 0.89 (s, 9H), −0.03 (s, 3 H), −0.15 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 157.5, 151.4, 145.4, 128.3, 127.2, 126.2, 122.5, 122.0, 112.0, 95.4, 74.8, 56.8, 40.9, 33.3, 26.1, 18.5, −4.4, −4.7; HRMS $(M+H)^+$ calcd for $C_{22}H_{32}INO_3Si$ 514.1274, found 514.1301.

**4.1.8. 6-[3-(*tert*-Butyldimethylsilanyloxy)-3-phenylpropyl]-3-methoxymethoxypyridine- 2-carbaldehyde (16).** To a solution of **15** (727 mg, 1.42 mmol) in THF (15 mL) at −78 °C was added *n*-BuLi (2.17 M in hexanes, 720 µl, 1.56 mmol) dropwise over 5 min. The resulting solution was stirred for additional 30 min and then ethyl formate (1.1 mL, 14 mmol) was added over 10 min. The reaction mixture was gradually warmed to 0 °C over 3 h and quenched with saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with ethyl acetate (3× 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (0 to 10% EtOAc in hexanes) gave 441 mg (75%) of **16** as a colorless oil; IR (neat) 2954, 2927, 2855, 1713, 1561, 1469, 1389, 1250, 1155, 1082, 973, 775, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 10.30 (s, 1 H), 7.54 (d, $J$=8.8 Hz, 1H), 7.31 (m, 5H), 7.26 (d, $J$=8.6 Hz, 1H), 5.29 (s, 2H), 4.76 (t, $J$= 5.4 Hz, 1H), 3.51 (s, 3H), 2.87 (m, 2H), 2.11 (m, 2H), 0.89 (s, 9H), 0.03 (s, 3H), −0.15 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 191.1, 156.1, 154.0, 145.4, 140.9, 128.3, 128.2, 127.2, 126.1, 124.9, 95.1, 74.8, 56.8, 40.8, 33.6, 26.1, 18.5, −4.4, −4.7; HRMS $(M+H)^+$ calcd for $C_{23}H_{33}NO_4Si$ 416.2257, found 416.2253.

**4.1.9. Bis-[6-[3-(*tert*-butyldimethylsilanyloxy)-3-phenylpropyl]-3-methoxymethoxypyridin-2-yl]-methanol (17).** To a solution of **15** (349 mg, 0.680 mmol) in THF (7 mL) at −78 °C was added *n*-BuLi (2.17 M in hexanes, 310 µl, 0.680 mmol) dropwise over 5 min. The resulting solution was stirred for 15 min, then compound **16** (311 mg, 0.748 mmol) in THF (5 mL) was added dropwise over 10 min. After the addition was complete, the reaction mixture was stirred at −78 °C for 2 h and then warmed gradually to 0 °C over 1 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ (50 mL) and extracted with ethyl acetate (3×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (0 to 10% EtOAc in hexanes) gave 371 mg (68%) of **17** as a colorless oil; IR (neat) 3375, 2954, 2928, 2856, 1580, 1469, 1403, 1361, 1255, 1155, 1081, 1056, 993, 836, 776 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.25 (m, 12H), 6.94 (d, $J$=6.2 Hz, 2H), 6.24 (d, $J$=4.3 Hz, 1H), 6.05 (bs, 1H), 4.98 (m, 4H), 4.74 (m, 2H), 3.19 (s, 3H), 3.18 (s, 3H), 2.75 (m, 4H), 2.03 (m, 4H), 0.91 (s, 18H), −0.02 (s, 6H), −0.14 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 153.3, 149.7, 148.9, 145.6, 128.1, 127.0, 126.0, 122.3, 121.9, 94.5, 74.7, 68.6, 58.8, 40.9, 33.2, 26.1, 18.4, −4.4, −4.7; HRMS $(M+H)^+$ calcd for $C_{45}H_{66}N_2O_7Si_2$ 803.4487, found 803.4510.

**4.1.10. Trifluoromethanesulfonic acid-6-[3-(*tert*-butyldimethylsilanyloxy)-3-phenylpropyl]-3-[6-[3-*tert*-butyldimethylsilanyloxy)-3-phenylpropyl]-3-trifluoromethanesulfonyloxypyridine-2-carbonyl]-pyridin-3-yl ester (18).** To a solution of **17** (348 mg, 0.434 mmol) in anhydrous $CH_2Cl_2$ (20 mL) was added activated $MnO_2$ (566 mg, 6.50 mmol), and the resulting mixture was stirred at rt for 30 h under an argon atmosphere. The residual manganese was removed by filtration (Celite). The filtrate was concentrated in vacuo. Purification by silica gel chromatography (10 to 20% EtOAc in hexanes) gave 347 mg (100%) of the desired ketone as a white foam; IR (neat) 2956, 2952, 2856, 1698, 1568, 1463, 1404, 1361, 1306, 1255, 1203, 1158, 1083, 981, 836, 777, 701 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.42 (d, $J$=8.6 Hz, 2H), 7.24 (m, 10H), 7.12 (d, $J$=7.7 Hz, 2H), 5.05 (s, 4H), 4.68 (t, $J$= 5.8 Hz, 2H), 3.34 (s, 6H), 2.74 (m, 4H), 1.97 (m, 4H), 0.88 (s, 18H), −0.03 (s, 6H), −0.18 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 193.4, 154.7, 150.8, 146.4, 145.5, 128.1, 127.0, 126.0, 125.2, 124.3, 95.3, 74.6, 56.3, 40.6, 33.3, 26.0, 18.4, −4.5, −4.8; HRMS $(M+H)^+$ calcd for $C_{45}H_{64}N_2O_7Si_2$ 801.4330, found 801.4311.

The above ketone (184 mg, 0.229 mmol) was dissolved in anhydrous $CH_2Cl_2$ (5 mL) and cooled to −78 °C. $Me_2BBr$ (2.01 M in $CH_2Cl_2$, 680 µl, 1.37 mmol) was added dropowise and the mixture was stirred at −78 °C for 4 h. Additional $Me_2BBr$ (2.01 M in $CH_2Cl_2$, 680 µl, 1.37 mmol) was then added. After stirring for 4 h, the mixture was cannulated into a vigorously stirred mixture of THF (10 mL) and saturated aqueous $NaHCO_3$ (15 mL) at 20 °C. After 5 min, the mixture was diluted with ethyl acetate (50 mL). The organic layer was separated and washed successively with $H_2O$ (50 mL), 10% aqueous sodium bisulfate (50 mL), and brine (50 mL). The combined aqueous layers were extracted with ethyl acetate (2× 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by flash chromatography (10 to 20% EtOAc in hexanes) gave 144 mg (88%) of the desired bisphenol as a colorless oil; IR (neat) 3362, 2968, 2857, 1623, 1594, 1464, 1257, 1173, 1084, 972 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.42 (d, $J$=8.6 Hz, 2H), 7.29 (m, 14H), 4.78 (t, $J$=5.8 Hz, 2H), 2.88 (m, 4H), 2.13 (m, 4H), 0.90 (s, 18H), 0.03 (s, 6H), −0.14 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 195.4, 156.8, 152.9, 145.1, 136.5, 130.1, 129.9, 128.3, 127.2, 126.1, 74.6, 40.7, 33.3, 26.1, 18.4, −4.4, −4.8; HRMS $(M+H)^+$ calcd for $C_{41}H_{56}N_2O_5Si_2$ 713.3806, found 713.3800.

A solution of the above bisphenol (107 mg, 0.150 mmol) and pyridine (120 µl, 1.50 mmol) in anhydrous $CH_2Cl_2$ (5 mL) was cooled to 0 °C under argon. A solution of freshly distilled triflic anhydride (130 µl, 0.750 mmol) in $CH_2Cl_2$ (1.0 mL) was added dropwise over a period of 5 min. The mixture was warmed to rt over 30 min and stirred for 16 h. The reaction mixture was filtered through Celite with $CH_2Cl_2$ and the solvent was removed in vacuo. Purification by silica gel chromatography (0 to 10% EtOAc in hexanes) gave 142 mg (97%) of **18** as a white foam; IR (neat) 2956, 2858, 1710, 1587, 1462, 1434, 1362, 1253, 1217, 1140,

1086 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.60 (d, $J$= 8.6 Hz, 2H), 7.33 (d, $J$=8.6 Hz, 2H), 7.25 (m, 10H), 4.68 (t, $J$=5.6 Hz, 2H), 2.81 (m, 4 H), 1.99 (m, 4H), 0.86 (s, 18H), −0.05 (s, 6H), −0.18 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 188.4, 162.0, 146.1, 145.0, 143.7, 130.3, 127.9, 127.2, 126.9, 126.0, 118.7 (q, $J$=1275 Hz), 74.2, 39.8, 33.2, 26.0, 18.4, −4.5, −4.9; $^{19}F$ NMR ($CDCl_3$, 300 MHz) $\delta$ −73.9; HRMS $(M+H)^+$ calcd for $C_{43}H_{54}F_6N_2O_9S_2Si_2$ 977.2792, found 977.2810.

**4.1.11. 2,7-Bis-3-phenyl-10-oxa-1,8-diazoniacyclopentaneanthracene-9-one bistrifluromethanesulfonate salt (2).** To a solution of **18** (416 mg, 0.426 mmol) in anhydrous DMF (10 mL) at rt was added $Ni(COD)_2$ (123 mg, 0.447 mmol). The resulting mixture was heated to 60 °C for 48 h, and then saturated aqueous $NaHCO_3$ (50 mL) was added. The reaction mixture was extracted with $CH_2Cl_2$ (3×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (0 to 10% EtOAc in hexanes) gave 196 mg (66%) of the desired cyclic ketone product as a yellow solid: mp 170–173 °C; IR (neat) 2928, 2856, 1685, 1466, 1258, 1092, 836, 776, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.75 (d, $J$=8.7 Hz, 2H), 7.59 (d, $J$=8.6 Hz, 2H), 7.28 (m, 10H), 4.81 (t, $J$=5.8 Hz, 2H), 3.08 (m, 4H), 2.14 (m, 4H), 0.89 (s, 18H), −0.03 (s, 6H), −0.15 (s, 6H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 175.3, 160.7, 151.9, 145.3, 137.9, 128.7, 128.3, 127.2, 126.1, 74.9, 41.0, 34.7, 26.1, 18.4, −4.4, −4.7; HRMS $(M+H)^+$ calcd for $C_{41}H_{54}N_2O_4Si_2$ 695.3700, found 695.3736.

A solution of the above ketone (45 mg, 0.064 mmol) in THF (1.0 mL) was cooled to 0 °C. Tetrabutylammonium fluoride (1.0 M in THF, 380 µl, 0.384 mmol) was added dropwise over a period of 10 min. The reaction was warmed to rt over a period of 30 min and stirred for an additional 1 h. The mixture was poured into saturated aqueous $NH_4Cl$ (20 mL) and extracted with EtOAc (3×20 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (30 to 50% EtOAc in hexanes) gave 25.0 mg (83%) of the desired diol as a colorless oil; IR (neat) 3384, 3067, 2926, 1676, 1604, 1469, 1266, 1124, 1061 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.82 (d, $J$= 8.7 Hz, 2H), 7.58 (d, $J$=8.6 Hz, 2H), 7.30 (m, 10H), 4.85 (t, $J$=5.8 Hz, 2H), 3.41 (bs, 2H), 3.15 (m, 4H), 2.27 (m, 4H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 175.0, 160.3, 151.9, 145.0, 137.6, 129.2, 128.5, 127.6, 127.4, 126.1, 73.7, 38.7, 34.5; HRMS $(M+H)^+$ calcd for $C_{29}H_{26}N_2O_4$ 467.1971, found 467.1989.

A solution of the above diol (25.0 mg, 0.0536 mmol) in anhydrous $CH_2Cl_2$ (2.0 mL) was cooled to 0 °C under argon. *N*,*N*-Diisopropylethylamine (20 µl, 0.12 mmol) was added and the reaction mixture was stirred for 15 min at 0 °C. A solution of freshly distilled triflic anhydride (15 µl, 0.085 mmol) in $CH_2Cl_2$ (1.0 mL) was added dropwise over a period of 5 min. The reaction mixture was warmed to rt over 30 min and stirred for 16 h. The mixture was filtered through Celite with $CH_2Cl_2$ and the solvent was removed in vacuo. Purification by HPLC (Whatman Partisil 10 C-8 column, 50% $H_2O/CH_3CN$, 2.0 mL/min) gave 50.0 mg (128%) of the desired crude product **2** as a purple solid; $^1H$ NMR ($CD_3CN$, 300 MHz) $\delta$ 8.99 (t, $J$=7.1 Hz, 1H), 8.50 (t, $J$=6.7 Hz, 1H), 8.23 (m, 1H), 7.25 (m, 2H), 7.15 (m, 1H), 6.98 (m, 1H), 6.69 (bs, 1H), 4.80 (t, $J$=5.1 Hz, 1H), 3.54 (t, $J$=5.2 Hz, 1H).[14]

**4.1.12. 5-Benzoyl-6-oxy-3-phenyl-2,3-dihydro-1*H*-indolizinylium Zwitter ion (19).** To a solution of **15** (64 mg, 0.13 mmol) in THF (2.0 mL) at −78 °C was added *n*-BuLi (2.28 M in hexanes, 60 µl, 0.14 mmol) dropwise over 5 min. The resulting solution was stirred for 15 min, and benzoyl chloride (150 µl, 1.25 mmol) was added over 10 min. The reaction was stirred at −78 °C for 2 h and then warmed to 0 °C over 1 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ (20 mL), and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (0 to 10% EtOAc in hexanes) gave 42.0 mg (69%) of the desired ketone as a colorless oil; IR (neat) 2954, 2928, 2855, 1681, 1459, 1255, 1155, 1082, 979, 836 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.86 (d, $J$= 7.9 Hz, 2H), 7.46 (m, 5H), 7.27 (m, 3H), 7.17 (d, $J$=8.4 Hz, 2H), 5.10 (s, 2H), 4.75 (t, $J$=5.9 Hz, 1H), 3.36 (s, 3H), 2.82 (m, 2H), 2.08 (m, 2H), 0.88 (m, 9H), 0.00 (s, 3H), −0.17 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 194.2, 155.1, 149.7, 146.9, 145.5, 136.6, 133.6, 130.5, 128.5, 128.2, 127.1, 126.1, 124.5, 124.0, 95.2, 74.8, 56.5, 40.8, 35.5, 26.1, 18.5, −4.4, −4.7; HRMS $(M+H)^+$ calcd for $C_{29}H_{37}NO_4Si$ 492.2570, found 492.2563.

A solution of the above ketone (308 mg, 0.626 mmol) in THF (10 mL) was cooled to 0 °C. Tetrabutylammonium fluoride (1.0 M in THF, 3.8 mL, 3.8 mmol) was added dropwise over a period of 10 min. After the addition was complete, the reaction mixture was warmed to rt over a period of 30 min and stirred for an additional 1 h. The reaction mixture was poured into saturated aqueous $NH_4Cl$ (50 mL) and extracted with EtOAc (3×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated in vacuo. Purification by silica gel chromatography (50 to 100% EtOAc in hexanes) gave 186 mg (80%) of the desired alcohol product as a colorless oil; IR (neat) 3406, 2923, 1675, 1596, 1461, 1255, 1154, 1081, 976 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.84 (d, $J$=7.7 Hz, 2H), 7.50 (m, 5H), 7.26 (m, 3H), 7.19 (d, $J$= 7.7 Hz, 2H), 5.08 (s, 2H), 4.65 (t, $J$=5.9 Hz, 1H), 3.80 (bs, 1H), 3.33 (s, 3H), 2.87 (m, 2H), 2.11 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 193.8, 154.4, 149.7, 146.5, 144.9, 136.3, 133.6, 130.2, 128.5, 128.3, 128.3, 127.2, 124.9, 124.2, 95.0, 73.4, 56.4, 38.6, 33.3; HRMS $(M+H)^+$ calcd for $C_{23}H_{23}NO_4$ 378.1705, found 378.1702.

A solution of the above alcohol (78.0 mg, 0.207 mmol) in anhydrous $CH_2Cl_2$ (4 mL) was cooled to 0 °C under argon. *N*,*N*-Diisopropylethylamine (40 µl, 0.23 mmol) was added and the reaction mixture was stirred for 15 min at 0 °C. A solution of freshly distilled triflic anhydride (40 µl, 0.227 mmol) in $CH_2Cl_2$ (1.0 mL) was added dropwise over a period of 5 min. The reaction mixture warmed to rt over 30 min and stirred for 1 h. The reaction mixture was filtered through Celite with $CH_2Cl_2$ and the solvent removed in vacuo. Purification by flash chromatography (silica gel) with 0–30% MeOH/EtOAc gave 43.3 mg (67%) of **19** as a

colorless oil; IR (neat) 3383, 1646, 1595, 1542, 1480, 1412, 1369, 1221, 1143, 1005 $cm^{-1}$; $^1H$ NMR ($CD_3OD$, 300 MHz) $\delta$ 7.65 (d, $J=9.1$ Hz, 1H), 7.53 (d, $J=9.1$ Hz, 1H), 7.44 (d, $J=7.5$ Hz, 2H), 7.37 (d, $J=7.3$ Hz, 1H), 7.20 (t, $J=7.7$ Hz, 2H), 7.03 (t, $J=7.9$ Hz, 2H), 6.95 (m, 3H), 6.24 (dd, $J=4.4$, 4.9 Hz, 1H), 3.55 (m, 1H), 3.38 (m, 1H), 2.91 (m, 1H), 2.30 (m, 1H); $^{13}C$ NMR ($CD_3OD$, 75 MHz) $\delta$ 193.0, 168.0, 142.9, 140.7, 139.6, 137.1, 136.4, 134.6, 130.5, 130.0, 129.9, 129.1, 128.5, 125.5, 74.1, 32.0, 31.2; HRMS $(M+H)^+$ calcd for $C_{21}H_{17}NO_2$ 316.1338, found 316.1346.

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## References and notes

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