Syntheses of 3-[(Alkylamino)methylene]-6-methylpyridine-2,4(1*H*,3*H*)-diones, 3-Substituted 7-Methyl-2*H*-pyrano[3,2-*c*]pyridine-2,5(6*H*)-dione Fluorescence Probes, and Tetrahydro-1*H*,9*H*-2,10-dioxa-9-azaanthracen-1-ones

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Abstract: Various condensation and ring-closing reactions were used for the syntheses of 3-[(alkylamino)methylene]-6-methylpyridine-2,4(1*H*,3*H*)-diones, bicyclic pyridinones, and tricyclic morpholinopyrones. For instance, 3-[(dialkylamino)methylene]-6-methylpyridine-2,4(1*H*,3*H*)-diones were synthesized from the condensation of dialkylamines and 3-formyl-4-hydroxy-6-methylpyridin-2(1*H*)-one. 3-Formyl-4-hydroxy-6-methylpyridin-2(1*H*)-one, derived from 3-formyl-4-hydroxy-6-methylpyridin-2(1*H*)-one, was used to construct a number of bicyclic pyridinones via a one-pot Knoevenagal and intramolecular lactonization reaction. Tricyclic morpholinopyrones were assembled from a dialkylation reaction involving a dinucleophile, 3-amino-4-hydroxy-6-methyl-2*H*-pyran-2-one, and a dielectrophile, *trans*-3,6-dibromocyclohexene. Depending on the reaction conditions, isomers of the tricyclic molecules can be selectively produced, and their chemical structures were unequivocally determined using single-crystal X-ray analyses and 2D COSY spectroscopy. The fluorescently active bicyclic pyridinone compounds show longer absorption (368–430 nm; maximum) and emission wavelengths (450–467 nm) than those of 7-amino-4-methylcoumarin (AMC; $\lambda_{abs,max}$ = 350 nm; λ_{em} = 430 nm) suggesting these molecules, such as 3-(2-aminoacetyl)-7-methyl-2*H*-pyrano[3,2-*c*]pyridine-2,5(6*H*)-dione, can be employed as fluorescence activity based probes for tracing biological pathways.

Key words: dialkylation, fluorescence probes, heterocycles, 3-substituted 7-methyl-2*H*-pyrano[3,2-*c*]pyridine-2,5(6*H*)-diones, tetrahydro-1*H*,9*H*-2,10-dioxa-9-azaanthracen-1-ones

In an effort to find new structures differing from the tricyclic pyrone pharmacophore,[1,2] we investigated various mono- and bicyclic pyridinone and tricyclic morpholinopyridinone molecules that may possess bioactivity.[1,2] Although several methods have been reported for the preparation of bicyclic pyridinones,[3–7] a method for the synthesis of tricyclic morpholinopyrones (such as **13**–**16**; Figure 1) is not available. Herein, we described a number of reactions including the coupling of 3-formyl-4-hydroxypyridin-2(1*H*)-one (**19**) with secondary amines to produce exocyclic enamines and with α-sulfinyl, α-sulfonyl, and α-keto esters to afford bicyclic pyridinones, and ring-closing reactions of 3-amino-4-hydroxy-2*H*-pyran-2-ones with *trans*-3,6-dibromocyclohexene to give tricyclic morpholinopyrones. Bicyclic pyridinones possess strong fluorescence activity at wavelengths of 450–467 nm, which are suitable for activity-based probes[8] and activity-based proteomics studies.[9]

In the search for new heterocyclic molecules possessing biological activity, monocyclic pyridinones **1**–**7**, bicyclic pyridinones **8**–**12**, and tricyclic morpholinopyrones **13**–**16** were synthesized (Figure 1). Since the synthesis of a monocyclic pyridinone, 6-methyl-3-[(phenylamino)methylene]pyridine-2,4(1*H*,3*H*)-dione (**18**), has been reported through the coupling reaction of 4-hydroxy-6-methylpyridin-2(1*H*)-one (**17**), triethyl orthoformate, and aniline,[4] we treated compound **17** with primary amines such as benzylamine and adenine separately under similar reaction conditions, and found that monocyclic pyridinones **1** and **3**, respectively, formed in 68% and 50% yields (Scheme 1). In the case of adenine, the C6-primary amino function appears to react faster than the C9-secondary amino group. In both cases a mixture of stereoisomers (*Z* and *E* at the enamine function) formed in an inseparable 1:4.5 ratio for compound **1** and a 1:2 ratio for compound **3**, based on NMR spectral data. The regiochemistry of compound **3** was determined from its 2D COSY NMR spectrum in which the enamine C7H of the major isomer at δ = 9.55 (d, *J* = 12 Hz) correlates with C6′-NH at δ = 13.95 (d, *J* = 12 Hz) and that of the minor isomer at δ = 9.51 (d, *J* = 12.9 Hz) correlates with C6′-NH at δ = 12.82 (d, *J* = 12.9 Hz); N1- and N9′-hydrogens of **3** appear as broad singlets. However this three-component coupling reaction appears to be applicable only with primary amines, when a secondary amine such as piperidine was used under similar reaction conditions no condensation product, i.e. monocyclic pyridinone **4**, was found.

To overcome this problem, we utilized 3-formyl-4-hydroxy-6-methylpyridin-2(1*H*)-one (**19**), which pre-installed with a carbaldehyde function at C3 of the pyridinone, as our starting material in a two-component condensation reaction with various secondary amines (Scheme 1). Aldehyde **19** was prepared according to a

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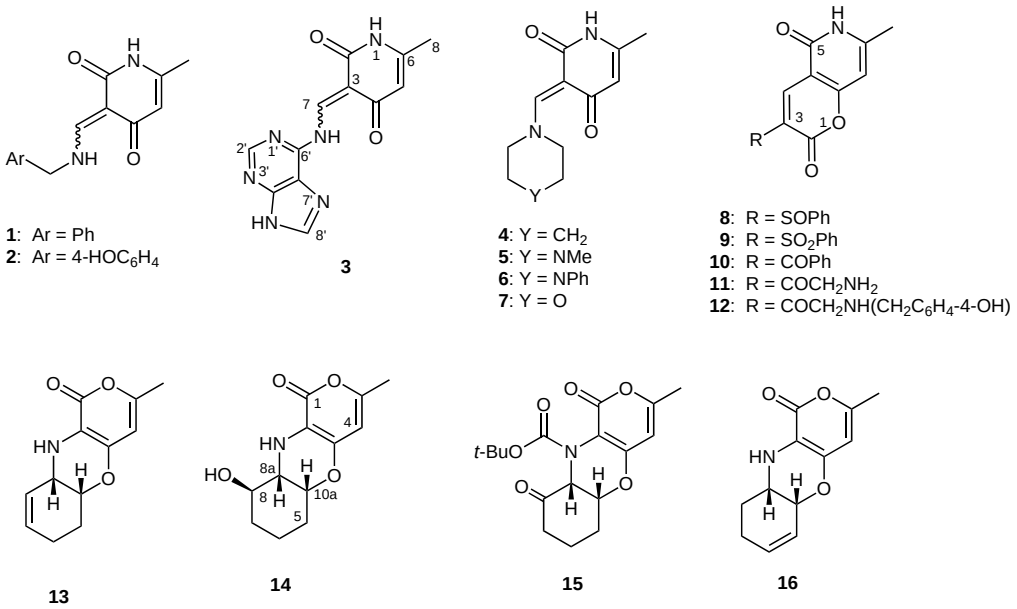
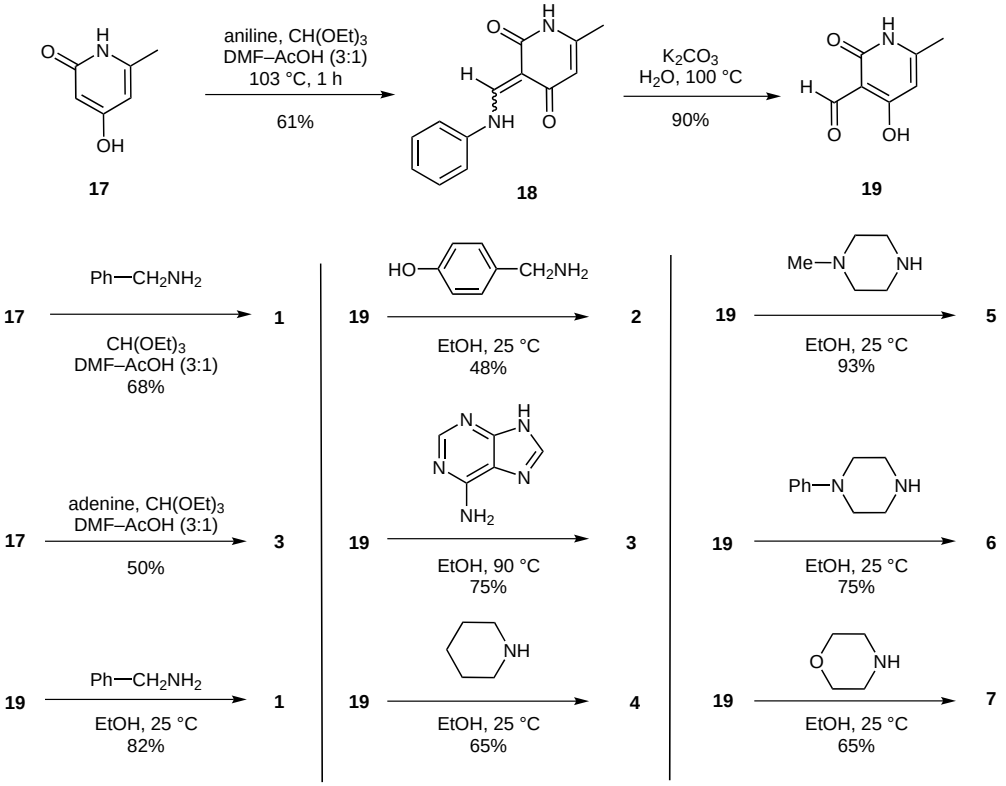


Figure 1 Synthesized monocyclic pyridinones **1**–**7**, bicyclic pyridinones **8**–**12**, and tricyclic morpholinopyrones **13**–**16**

previously established synthetic route starting from pyridinone **17**[4] as described in Scheme 1.

The enamine intermediate **18**, formed as a 4:1 mixture of *E*- and *Z*-isomers, was hydrolyzed using aqueous potassium carbonate at 100 °C to provide aldehyde **19** (90% yield). The spectral data for aldehyde **19** are similar to those previously reported.[4] Various monocyclic pyridinone enamines, **1**–**7**, were synthesized in good to excellent yields by treating aldehyde **19** with primary and secondary amines in ethanol (Scheme 1). Compounds **1**, **2**, and **4**–**7** could be obtained at room temperature by treating aldehyde **19** with benzylamine, 4-hydroxybenzylamine, piperidine, *N*-methylpiperazine, *N*-phenylpiperazine, and morpholine, respectively, however, condensa-



Scheme 1 Synthesis of monocyclic pyridinones **1**–**7**

tion with adenine to form compound **3** required an elevated temperature to achieve product formation. During the course of the reaction, compounds **1**–**6** precipitated out from the ethanolic reaction solvent, which facilitated product formation and isolation, however, compound **7** remained soluble and hence 2–3 equivalents of morpholine were necessary to drive product formation and a longer reaction time was required. The ^{1}H NMR spectral data of compounds **4**–**7** show the presence of single stereoisomers and that of compounds **1**–**3** indicate two stereoisomers. The stereochemistry of **4**–**7** was not determined. Single crystals of the major stereoisomer of **1** could be grown by slow cooling and evaporation in ethanol. An ORTEP diagram of compound **1** from a single-crystal X-ray analysis is shown in Figure 2, which unequivocally determined the *E* enamine double bond geometry of **1** (NMR spectrum of the single crystals confirms it to be the major stereoisomer). Selected bond lengths and bond angles of compounds **1**, **13**, and **16** derived from single-crystal X-ray structure analyses are listed in Table 1.

Aldehyde **19** proved to be a versatile scaffold[4] through which to construct various bicyclic pyridinone structures by treating it with various doubly activated esters such as methyl α-(phenylsulfinyl)acetate, methyl α-(phenylsulfonyl)acetate, ethyl 3-oxo-3-phenylpropanoate, γ-(Boc-amino)-β-keto ester **20**,[10] and β-keto ester **22** in refluxing ethanol, employing piperidine as the catalyst (Scheme 2). The mechanism by which compounds **8**–**12** are formed is expected to proceed via Knoevenagel condensation[4] of the ester with aldehyde **19** followed by intramolecular lactone formation. Notably, the ester function is required to orient at the *cis* configuration with the phenolic OH group for the lactonization. When one equivalent of piperidine was used, byproduct **4** formed predominantly. The bicyclic pyridinones **8**, **9**, and **10** could be obtained in 69%, 81%, and 100% isolated yields, respectively, after filtration of the products from the crude reaction mixtures or column chromatography on silica gel. The bicyclic pyridinone **11** containing an amino function in the side chain was obtained in 45% overall yield from the coupling of **19** and **20**[10] followed by removal of the Boc protecting group of **21** with trifluoroacetic acid.

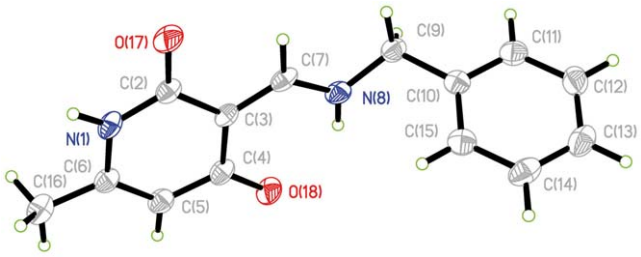


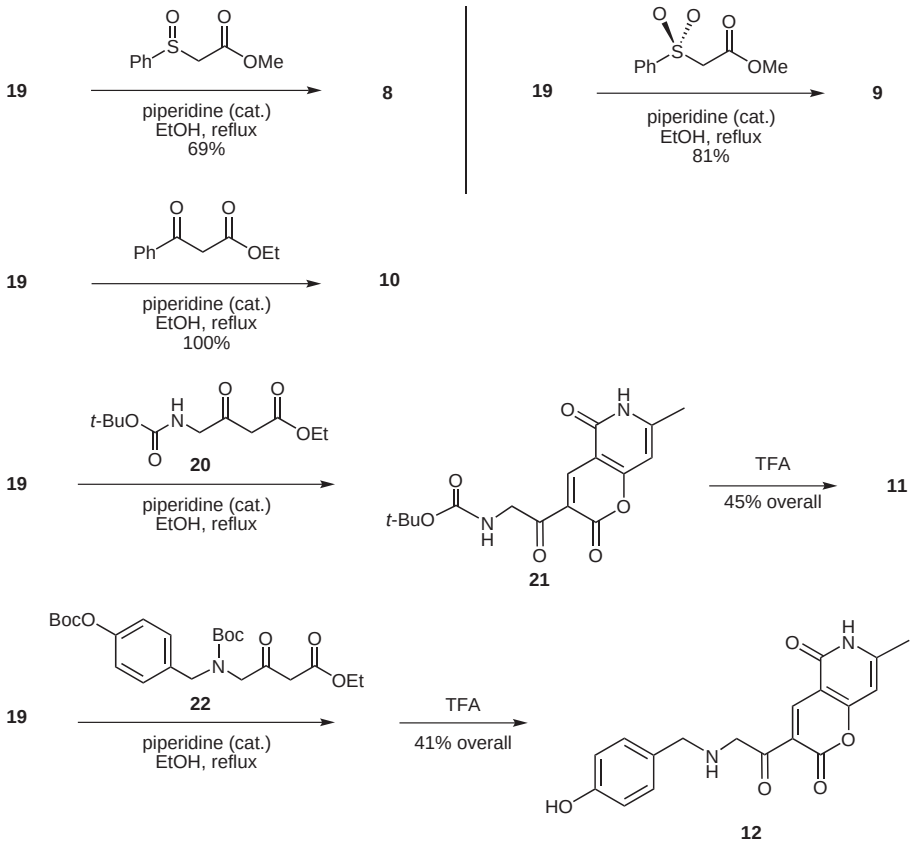
Figure 2 An ORTEP drawing of a single-crystal X-ray structure of (*E*)-3-[(benzylamino)methylene]-6-methylpyridine-2,4(1*H*,3*H*)-dione (**1**) (CCDC 989745); $C_{14}H_{14}N_2O_2$, triclinic, space group *P*-1, *Z* = 2, *R*1 factor 0.0702.

Similarly, coupling of **19** and β-keto ester **22** followed by Boc deprotection gave compound **12**. Compound **22** was prepared by modifying the reported synthesis of compound **20**.[10] The amino function of **11** or **12** can condense with the carboxylic acid group of various amino acids or peptides to generate fluorescence-active molecules.

Molecules containing tricyclic pyrone scaffolds have been synthesized in our laboratory and have been shown to possess strong cell protective action against oligomeric amyloid β peptide toxicity[1,11] and antiviral activity.[2] To explore new structures, a tricyclic pyrone scaffold

Table 1 Selected Bond Lengths and Bond Angles of Compounds **1**, **13**, and **16** from Single-Crystal X-ray Structure Analyses

Compound **1**		Compound **13**		Compound **16**	
Bond lengths (Å)	Bond angles (°)	Bond lengths (Å)	Bond angles (°)	Bond lengths (Å)	Bond angles (°)
N(1)–C(2) 1.362(3)	C(2)–N(1)–C(6) 124.60(19)	C(1)–O(12) 1.2236(15)	O(2)–C(1)–C(9A) 117.48(10)	C(1)–O(12) 1.2239(17)	O(12)–C(1)–O(2) 117.12(12)
N(1)–C(6) 1.386(3)	O(17)–C(2)–N(1) 119.57(19)	C(1)–O(2) 1.3749(15)	C(3)–O(2)–C(1) 122.73(10)	C(1)–O(2) 1.3757(17)	C(1)–O(2)–C(3) 122.99(11)
C(2)–O(17) 1.258(2)	O(17)–C(2)–C(3) 124.0(2)	C(1)–C(9A) 1.4283(16)	C(3)–C(4)–C(4A) 119.39(11)	C(1)–C(9A) 1.4395(18)	C(3)–C(4)–C(4A) 119.23(13)
C(2)–C(3) 1.446(3)	N(1)–C(2)–C(3) 116.38(19)	O(2)–C(3) 1.3686(15)	C(7)–C(8)–C(8A) 123.73(12)	O(2)–C(3) 1.3764(17)	C(6)–C(5)–C(10A) 123.20(14)
C(3)–C(7) 1.387(3)	C(7)–C(3)–C(2) 116.65(19)	C(3)–C(4) 1.3446(17)	N(9)–C(8A)–C(8) 113.59(11)	C(3)–C(4) 1.3476(19)	C(5)–C(6)–C(7) 123.53(13)
C(3)–C(4) 1.448(3)	C(5)–C(4)–C(3) 116.64(19)	C(4)–C(4A) 1.4235(17)	N(9)–C(8A)–C(10A) 108.92(10)	C(4)–C(4A) 1.4269(19)	N(9)–C(8A)–C(8) 113.03(13)
C(4)–O(18) 1.257(3)	N(8)–C(7)–C(3) 127.3(2)	C(7)–C(8) 1.3314(19)	O(10)–C(10A)–C(8A) 111.68(10)	C(5)–C(6) 1.332(2)	N(9)–C(8A)–C(10A) 110.16(11)
C(7)–N(8) 1.303(3)	C(7)–N(8)–C(9) 123.29(19)	N(9)–C(9A) 1.3955(16)	C(5)–C(10A)–C(8A) 111.43(11)	C(8A)–C(10A) 1.533(2)	C(9A)–N(9)–C(8A) 119.03(12)



Scheme 2 Synthesis of bicyclic pyridinones **8**–**12**

containing a nitrogen atom in the central ring (such as **13**) would provide additional hydrogen bond donor (N–H) capacity. We therefore examined a two-component coupling reaction for the synthesis of tricyclic morpholinopyrones from dinucleophile 3-aminopyrone **23** and dielectrophile *trans*-3,6-dibromocyclohexene (**25**).[12] The expeditious synthesis started from commercially available 4-hydroxy-6-methyl-2*H*-pyran-2-one, which was converted into 3-aminopyrone **23** via a two-step process,[13] involving the nitration of 4-hydroxy-6-methyl-2*H*-pyran-2-one at C3 by nitric acid/sulfuric acid followed by reduction of the resulting nitro function to amine over hydrogen/palladium, in 62% overall yield. To examine the two-component ring-closing reaction, we first study N-protected pyrone **24**. Aminopyrone **23** was capped with a *tert*-butoxycarbonyl protecting group to afford Boc-aminopyrone **24** in 57% yield (Scheme 3). Upon treatment of pyrone **24** with one equivalent of sodium hydride followed by dibromide **25**, Boc-tricyclic morpholinopyrone **27** resulted in 25% yield, and no other isomers were found (Table 2, entry 1). We envision that the initial step requires deprotonation of **24** with sodium hydride to form a pyrone oxy anion, which upon treatment with dibromide **25** supposedly forms O-alkylated intermediate **26**. This O-alkylated intermediate undergoes a ring-closing reaction to give **27**. The Boc protecting group of **27** was readily removed using 10% trifluoroacetic acid in dichloromethane at 40 °C to furnish tricyclic morpholinopyrone **13** in quantitative yield. Only the *cis*-diastereomer **13** was detected from the cyclization reaction and the stereochemistry was unequivocally determined through a single-crystal X-ray structure analysis (Figure 3). Single crystals of tricyclic morpholinopyrone **13** were achieved by slow evaporation of a solution of **13** in ethanol. The crystal structure shows that the tricyclic scaffold forms a *cis*-fused ring junction upon cyclization and the double bond is situated between C7 and C8 implying a S_N2' reaction takes place from intermediate **26** with retention of configuration. The two synclinal bridgehead protons have a torsion angle of 48.1°.

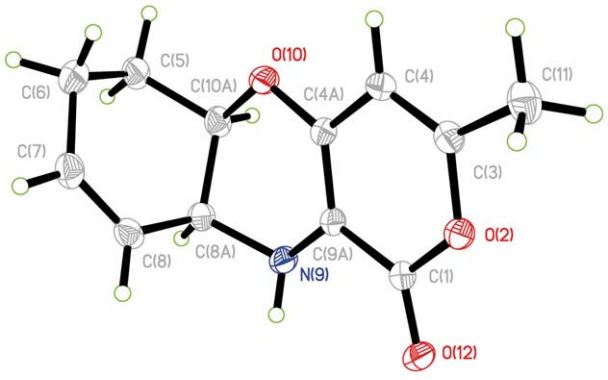
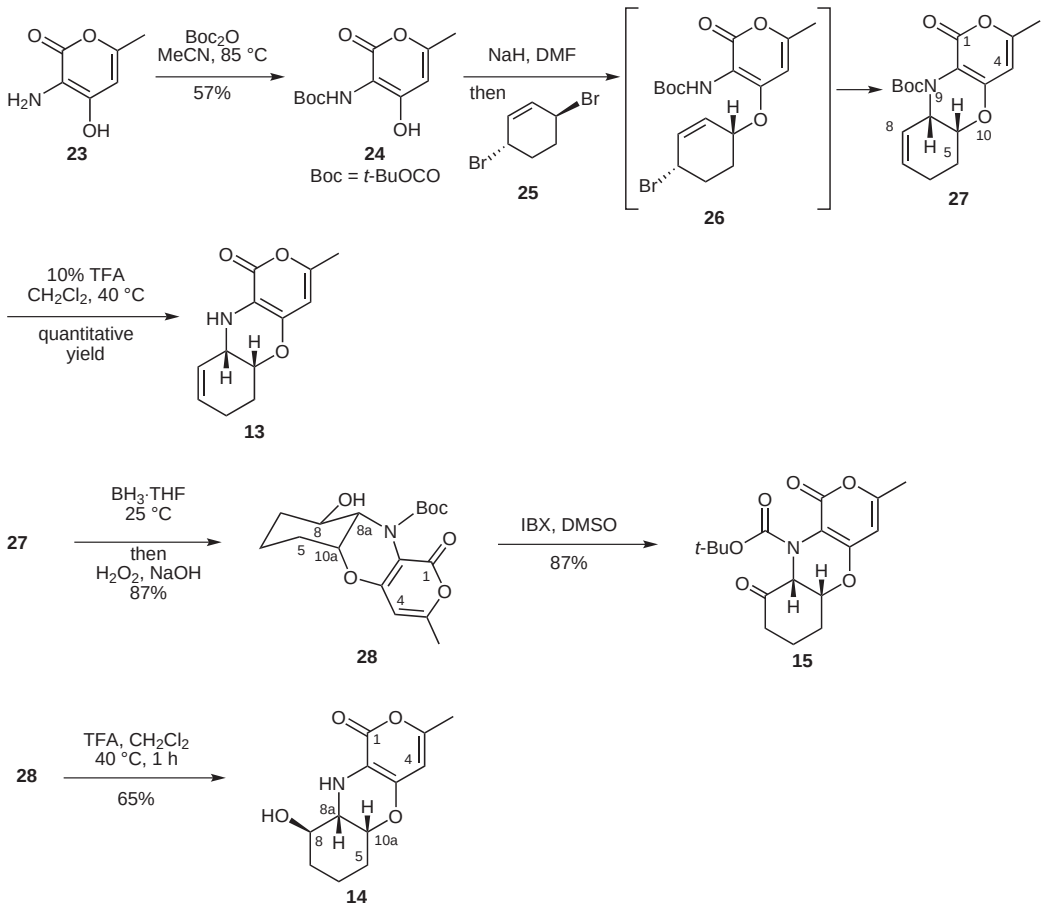


Figure 3 An ORTEP drawing of a single-crystal X-ray structure analysis of 3-methyl-5,8a,9,10a-tetrahydro-1*H*,6*H*-2,10-dioxa-9-azaanthracen-1-one (**13**) (CCDC 989746); $C_{12}H_{13}NO_3$, monoclinic, space group $P2_1/c$, $Z = 4$, and $R1$ factor 0.0538.

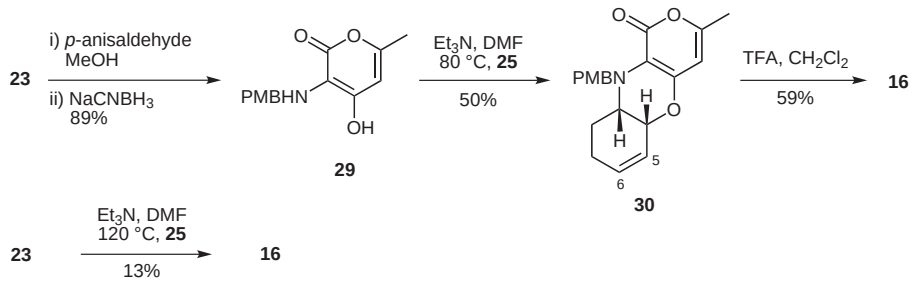
Dibromide **25** was prepared from a one-step double bromination of cyclohexene with *N*-bromosuccinimide (2 equiv)[14] and the *trans*-stereochemistry was verified by comparing its ^{1}H NMR spectral data with the literature values.[12] We have also obtained a single-crystal X-ray structure of this compound which agrees with that reported.[12] The presence of a double bond in the six-membered carbocyclic ring of the tricyclic skeleton is significant because it allows for further modification of the tricyclic scaffold as demonstrated in Scheme 3. The double bond of **27** was regioselectively hydroxylated by employing standard hydroboration/oxidation conditions to give 8-hydroxy tricyclic morpholinopyrone **28** as a single stereoisomer. The stereochemistry at C8 was assumed in that borane approaches the C7–C8 double bond from the least hindered face (same side of C8aH and C10aH).

The regiochemistry of the C8 hydroxy function was assigned from the appearances of C8H at δ = 3.33 showing a triplet of doublets with J = 10.5 and 3.5 Hz, C8aH at δ = 4.22 showing a doublet of doublets with J = 10.1 and 3.5 Hz, and C10aH at δ = 4.40 showing a quartet with J = 3.5 Hz, suggesting C8H orients at the axial, C8aH at axial, and C10aH at equatorial position based on the J values. The chemical shift assignments and couplings were supported from the 2D COSY, HMBC, and HSQC spectra of **28**. The regiochemistry at C8 was further verified from the oxidation of **28** to ketone **15** using 2-iodoxybenzoic acid in dimethyl sulfoxide. Only two alkanyl downfield hydrogens at δ = 5.20 (d, J = 4 Hz, C8aH) and 4.75 (q, J = 4 Hz, C10aH) were found in the ^{1}H NMR spectrum of **15**. The Boc protecting group of **28** can be removed by 10% trifluoroacetic acid in dichloromethane at 40 °C to give 8-hydroxy tricyclic morpholinopyrone **14**. These results are encouraging because the alkene, hydroxy, and ketone functionalities provide a means for further structural modification of the tricyclic ring system making further synthesis of analogues possible.

Intriguing differences were observed in the aforementioned double alkylation reaction for the formation of a tricyclic morpholinopyrone scaffold. A regioisomer of **27**, **30**, was found when a different protecting group, *p*-methoxybenzyl (PMB), was used (Scheme 4). The PMB group was installed via a two-step reductive amination procedure[1] by treating 3-aminopyrone **23** with *p*-anisaldehyde in methanol followed by sodium cyanoborohydride and acetic acid in ethanol to give **29** in 89% yield. Various reaction conditions were examined for the dialkylation reactions and results are summarized in Scheme 5 and Table 2. A single diastereomer of the olefin regioisomer **30** resulted when treating **29** with dibromide **25** and triethylamine in 50% isolated yield (Table 2, entry 5) after column chromatographic purification. No other isomers

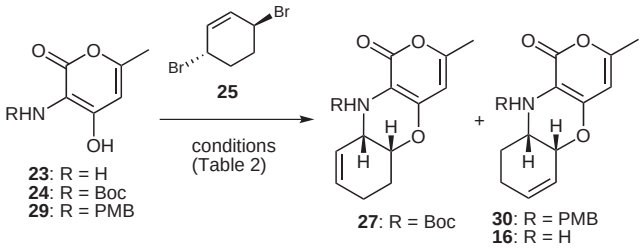


Scheme 3 Synthesis of tricyclic morpholinopyrones **13**–**15**



Scheme 4 Synthesis of tricyclic morpholinopyrone **16**

were found. When sodium hydride was used in place of triethylamine in the above double alkylation reaction, only 7% yield of **30** was obtained (entry 4). The PMB group was removed by 5% trifluoroacetic acid in dichloromethane at 40 °C to give tricyclic morpholinopyrone **16**, which structure was unequivocally determined from a single-crystal X-ray structure analysis (Figure 4).



Scheme 5 Synthesis of tricyclic morpholinopyrones **27**, **30**, and **16**

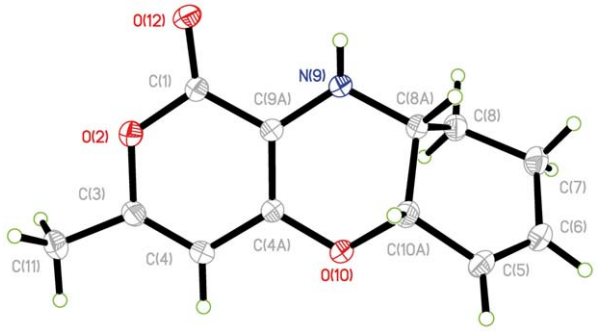


Figure 4 An ORTEP drawing of a single-crystal X-ray analysis of 3-methyl-7,8,8a,10a-tetrahydro-1*H*,9*H*-2,10-dioxa-9-azaanthracen-1-one (**16**) (CCDC 989747); $C_{12}H_{13}N_1O_3$, monoclinic, space group $P2_1/c$, $Z = 4$, and $R1$ factor 0.0595.

The tricyclic scaffold of **16** also formed a *cis*-fused ring junction upon cyclization and the two synclinal bridge head protons have a torsion angle of 44.2°. Of interest is the position of the double bond which is now found between C5 and C6. This suggests that the cyclization steps took place either via initial S_N2 N-alkylation of **29** with dibromide **25** followed by S_N2' nucleophilic substitution (with retention of configuration) by the hydroxy function, or by initial S_N2' O-alkylation of **29** with dibromide **25** (with retention of configuration) followed by ring closing due to S_N2 nucleophilic substitution (inversion) by the amine function. We further discovered that pyrone **16** can be synthesized in a single step (in a lower yield; Table 2, entry 7) by the direct treatment of amine **23** with dibromide **25** and triethylamine in *N*,*N*-dimethylformamide at 120 °C for two hours without PMB protection. Table 2 summarizes the reaction conditions that formed tricyclic morpholinopyrone scaffolds. The alkylation of Boc-protected pyrone **24** with **25** and potassium carbonate or triethylamine gave only 3% and 7% yield, respectively (entries 2 and 3). The protecting groups appear to affect the regiochemistry of the olefinic moiety of the tricyclic products. The use of Boc as an amine protecting group resulted in C7–C8 double bond isomer, while an amine substituent (with or without PMB protecting group) gave the C5–C6 double bond isomer. The strengths of the N–H acidities appear to affect the initial alkylation step, which resulted in different regioisomers. Notably, no tricyclic product was found when amine **23** was treated with sodium hydride or DBU and dibromide **25** (entries 6 and 9), and the use of other bases such as pyridine only produced trace amounts of **16** (entry 8).

Table 2 Reaction Conditions and Yields of the Formation of Tricyclic Morpholinopyrones **27**, **30**, and **16**

Entry	R	Conditions	Product	Yield (%)
1	Boc	(i) NaH, DMF; (ii) Et_3N, MeCN, 95 °C, 8 h	**27**	25
2	Boc	K_2CO_3, DMF, 90 °C, 8 h	**27**	3
3	Boc	Et_3N, DMF, 80 °C, 3 h	**27**	7
4	PMB	NaH, DMF–MeCN (1:1), 80 °C, 8 h	**30**	7
5	PMB	Et_3N, DMF, 80 °C, 2.5 h	**30**	50
6	H	(i) NaH, DMF; (ii) Et_3N, MeCN, 80 °C, 8 h	**16**	0
7	H	Et_3N, DMF, 120 °C, 2 h	**16**	13
8	H	pyridine, DMF, 120 °C, 0.5 h	**16**	2
9	H	DBU, DMF, 120 °C, 0.5 h		–

One of our goals in the synthesis of bicyclic pyridinones is the construction of new fluorescence activity based probes.[8,9] Based on the reported bicyclic heterocycles,[15] bicyclic pyridinones **8**–**12** should be fluorescently active. Indeed, Table 3 summarizes photophysical data from the UV absorption and fluorescence emission spectra of **8**–**12** and **21** showing longer absorption and fluorescence emission wavelengths compare with those of commercially available 7-amino-4-methylcoumarin (AMC; λ_{ex} = 351 nm; λ_{em} = 430 nm; $\lambda_{abs,max}$ = 350 nm in ethanol), a widely used fluorescence probe.[15] All five compounds possess similar fluorescence emission wavelengths, λ_{em}, of 450–467 nm and quantum yields, Φ_F, ranging from 0.03 to 0.54. Perylene was used as a standard for the calculation of quantum yields.[16] The C3 electron-withdrawing group such as sulfoxide, sulfone, and ketone of the bicyclic pyridinone system contributes bathochromic and bathofluoric shifts in the absorption and fluorescence spectra, respectively. The extended conjugation contributed from the phenyl ring of ketone **10** leads to a longer emission wavelength of 467 nm than other measured compounds, and sulfone **9** possesses the highest quantum yield.

Table 3 Photophysical Data for Absorption (abs) and Emission (em) of Compounds **8**–**12** and **21** in Methanol

Compounds	**8**	**9**	**10**	**11**	**12**	**21**	Perylene[a]
λ_{abs} (nm)[b]	368	385	381	427	430	393	436
log ε ($M^{-1}cm^{-1}$)[c]	4.16	4.26	4.18	3.85	3.67	4.18	4.40
λ_{ex} (nm)[d]	380	380	380	380	380	380	380
λ_{em} (nm)[e]	450	450	467	450	458	460	439
Φ_F[f]	0.03	0.54	0.03	0.14	0.06	0.22	0.94[g]

[a] Data were obtained in cyclohexane due to solubility.
[b] Wavelengths of maximum absorption.
[c] Extinction coefficient.
[d] Wavelengths of fluorescence excitation.
[e] Wavelengths of maximum fluorescence emission.
[f] Fluorescence quantum yields were calculated by following the reported method[16] from two independent experiments.
[g] Literature quantum yield of perylene is 0.94 (in cyclohexane).[16]

One-pot condensations of 3-formyl-4-hydroxy-6-methylpyridin-2(1*H*)-one (**19**) with secondary amines afforded various 3-[(dialkylamino)methylene]-6-methylpyridine-2,4(1*H*,3*H*)-diones and with α-sulfinyl, α-sulfonyl, and β-keto esters gave bicyclic pyridinones, which can be used as fluorescence probes for biochemical research. Moreover, one-pot dialkylation reactions of 3-amino-4-hydroxy-6-methyl-2*H*-pyran-2-ones with *trans*-3,6-dibromocyclohexene under various reaction conditions were investigated and different regioisomers can be selectively produced albeit in low yields. Bioactivity of the newly synthesized monocyclic, bicyclic, and tricyclic molecules will be evaluated and reported in due course.

All melting points are uncorrected. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were measured from a solution in $CDCl_3$ or DMSO-d_6 relative to TMS (δ = 0 ppm) or $CHCl_3$ (δ = 7.26 ppm) (^{1}H NMR) or $CDCl_3$ (δ = 77.0 ppm) or DMSO (δ = 39.5 ppm) (^{13}C NMR). The *E* and *Z* assignment in ^{13}C NMR spectral data are assumed and based on the signal intensities. LR-MS were taken from an API 2000-triple quadrupole ESI-MS/MS mass spectrometer. HRMS were obtained using a LCT Premier ToF mass spectrometer. IR spectra were measured directly in either solid or liquid form. UV-Vis absorption measurements were recorded on a Hewlett Packard 8453 UV-VIS spectrophotometer and fluorescence emission spectra were recorded on a Jobin Yvon-spec fluoromax-2 fluorescence spectrophotometer (slits: 2.5 nm; integration time: 0.5 s); fluorescence emission spectra excitation wavelength: 380 nm, and emissions: 400–600 nm. The fluorescence quantum yields were determined by following a procedure reported by Brouwer[16] using perylene (Φ_F = 0.94, cyclohexane) as the standard reference compound. Perylene was chosen as the reference because it has an emission wavelength similar to compounds **8**–**12** thus allowing the same excitation wavelength (380 nm) to be used for all molecules. Fluorescence emission spectra and UV-VIS absorption spectra for compounds **8**–**12**, and **21** were recorded at 2 μM and 20 μM, respectively, in (MeOH), and perylene recorded at 1 μM and 10 μM, respectively, in cyclohexane. Refractive indices for MeOH and cyclohexane were incorporated when calculating relative fluorescence quantum yields.[16] X-ray crystal structure data sets were collected on a Bruker Kappa APEX II systems using MoKα radiation. Data were collected using APEX2 software (APEXII v2009, Bruker Analytical X-ray Systems, Madison, WI). Data collection strategies were determined using COSMO (v1.60, 1999–2009, Bruker Analytical X-ray System, Madison, WI). Scan speed and scan width were chosen based on scattering power and peak rocking curves. All datasets were collected at –153 °C using an Oxford Cryostream low-temperature device. Unit cell constants and orientation matrix were improved by least-squares refinement of reflections threshold from the entire dataset. Integration was performed with SAINT (v7.60a, 1997–2008, Bruker Analytical X-ray System, Madison, WI), using this improved unit cell as a starting point. Precise unit cell constants were calculated in SAINT from the final merged dataset. Lorenz and polarization corrections were applied. Multiscan absorption corrections was performed with SADABS (v2008/1, Bruker Analytical X-ray System, Madison, WI). Data were reduced with SHELXTL (v2008/4, Bruker Analytical X-ray System, Madison, WI). The structures were solved in all cases by direct methods without incident. The molecules were fully ordered, no solvent was present, and no constraints or restraints were applied. Coordinates for N–hydrogen atoms were allowed to refine. All other hydrogen atoms were located in idealized positions and were treated with a riding model. Refinement was continued to convergence using the recommended weighting scheme. 4-Hydroxy-6-methylpyridin-2(1*H*)-one (**17**) and 4-hydroxy-6-methyl-2*H*-pyran-2-one were purchased from Fisher Scientific and Sigma-Aldrich, respectively. All solvents were dried over appropriated drying chemical such as CaH_2 (for DMF), Mg (for EtOH), or Na/benzophenone (for THF) followed by distillation. All low-molecular-weight amines were purified by distillation.

3-Formyl-4-hydroxy-6-methylpyridin-2(1*H*)-one (19)[4]

A solution of 4-hydroxy-6-methylpyridin-2(1*H*)-one (**17**, 8.0 g, 64 mmol), triethyl orthoformate (53 mL, 0.32 mol), and aniline (5.8 mL, 64 mmol) in DMF and AcOH (3:1, 60 mL) under argon was heated at 130 °C for 1 h. The solution was cooled to 25 °C, diluted with H_2O (300 mL), and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic layers were washed with brine and concentrated to dryness. Et_2O (200 mL) was added to the residue, the solution cooled to 0 °C, and the precipitated solid was collected by filtration, washed with Et_2O, and dried under vacuum to give 6-methyl-3-

[(phenylamino)methylene]pyridine-2,4(1*H*,3*H*)-dione (**18**)[4] (8.9 g, 61%, *E*/*Z* 4:1).

^{1}H NMR: δ = 9.76 (br s, 1 H, NH), 8.87 (d, *J* = 12.5 Hz, 1 H, =CHN, minor), 8.83 (d, *J* = 12.5 Hz, 1 H, =CHN, major), 7.45–7.25 (m, 5 H), 5.67 (s, 1 H, =CH, minor), 5.64 (s, 1 H, =CH, major), 2.20 (s, 3 H, major), 2.18 (s, 3 H, minor).

A solution of **18** (2.0 g, 8.7 mmol) and K_2CO_3 (40 g, 0.29 mol) in H_2O (800 mL) was heated at 100 °C for 4 h, cooled to 25 °C, acidified with concd HCl to pH 2, and extracted with CH_2Cl_2 (2 ×). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give **19** as a yellow solid; yield: 1.2 g (90%); mp 256 °C (dec.).[4]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.71 (s, 1 H, NH), 11.50 (br s, 1 H, OH), 10.08 (s, 1 H, CHO), 5.86 (s, 1 H, =CH), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 193.3, 174.7, 163.3, 157.1, 105.3, 97.7, 19.5.

MS (ESI, MeOH): *m*/*z* = 176.1 ([M + Na$^+$]).

3-[(Benzylamino)methylene]-6-methylpyridine-2,4(1*H*,3*H*)-dione (1); Typical Procedure for the Synthesis of Compounds 1–7

To a solution of **19** (1.31 mmol) in distilled EtOH (4 mL) under argon was added $BnNH_2$ (1.44 mmol), the mixture was stirred at 25 °C for 24 h, and the solution was diluted with hexane–Et_2O (1:1). The precipitated solid was collected by filtration, washed with hexane–Et_2O (1:1), and dried under vacuum to yield pure **1** as a yellow solid; yield: 0.26 g (82%); ratio *E*/*Z* 4.5:1; mp 219–221 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (major *E*-isomer) = 9.69 (br s, 1 H), 8.45 (d, *J* = 12 Hz, 1 H), 8.38 (s, 1 H), 7.23–7.45 (m, 5 H), 5.56 (s, 1 H), 4.65 (d, *J* = 4 Hz, 2 H), 2.13 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (major *E*-isomer) = 185.0, 166.9, 160.7, 149.3, 135.5, 129,3, 128.7, 127.8, 107.0, 102.5, 54.5, 20.0.

MS (ESI, MeOH): *m*/*z* = 265.4 ([M + Na$^+$]).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{14}N_2O_2Na$: 265.0953; found: 265.0946.

3-[(4-Hydroxybenzylamino)methylene]-6-methylpyridine-2,4(1*H*,3*H*)-dione (2)

Following the typical procedure using **19** (1.7 mmol) and 4-hydroxybenzylamine (1.7 mmol) in EtOH (2 mL) with stirring at 25 °C for 4 h gave **2** as a yellow solid; yield: 0.21 g (48%); ratio *E*/*Z* 7:3; mp 222–225 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.07–12.19 (m, 0.7 H, *E*), 10.91–11.01 (m, 0.3 H, *Z*), 10.27 (s, 1 H), 9.50 (s, 1 H), 8.29–8.36 (m, 1 H), 7.17 (d, *J* = 7.4 Hz, 2 H), 6.76 (d, *J* = 7.4 Hz, 2 H), 5.30 (s, 1 H), 4.54–4.61 (m, 2 H), 1.98 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 183.5 (*E*), 180.3 (*Z*), 166.9 (*Z*), 165.0 (*E*), 159.4 (*E*), 159.0 (*Z*), 157.1 (*E*/*Z*), 149.5 (*E*), 149.0 (*Z*), 129.5 (*E*/*Z*), 127.3 (*Z*), 127.1 (*E*), 115.5 (*E*/*Z*), 106.2 (*Z*), 105.1 (*E*), 101.5 (*E*), 101.4 (*Z*), 52.1 (*E*/*Z*), 19.1 (*E*/*Z*).

MS (ESI, MeOH): *m*/*z* = 281.3 ([M + Na]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_3$: 259.1083; found: 259.1107.

6-Methyl-3-[(9*H*-purin-6-ylamino)methylene]pyridine-2,4(1*H*,3*H*)-dione (3)

Following the typical procedure using **19** (1.31 mmol) and adenine (1.31 mmol) in EtOH (4 mL) with stirring at 90 °C for 14 h gave **3** as a yellow solid; yield: 0.27 g (75%); ratio *E*/*Z* 2:1); mp >300 °C (had not melted).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.95 (d, *J* = 12.0 Hz, 0.7 H, *E*), 13.75 (br s, 1 H, NH of *E* and *Z*), 12.82 (d, *J* = 12.9 Hz, 0.3 H, *Z*), 10.80 (br s, 0.3 H, NH of *Z*), 10.73 (br s, 0.7 H, NH of *E*), 9.55 (d, *J* = 12.0 Hz, 0.7 H, *E*), 9.51 (d, *J* = 12.9 Hz, 0.3 H, *Z*), 8.69 (s, 1 H, *E* and *Z*), 8.59 (s, 1 H, *E* and *Z*), 5.51 (s, 0.7 H, *E*), 5.48 (s, 0.3 H, *Z*), 2.08 (s, 2.1 H, *E*), 2.07 (br s, 0.9 H, *Z*).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 193.3 (*E*/*Z*), 185.1 (*E*/*Z*), 180.8 (*E*/*Z*), 174.7 (*Z*), 167.6 (*E*), 153.5 (*E*), 152.4 (*Z*), 151.9 (*E*/*Z*), 150.4 (*E*), 149.7 (*Z*), 146.8 (*Z*), 144.4 (*E*), 122.3 (*Z*), 106.5 (*Z*), 106.4 (*E*), 105.1 (*E*/*Z*), 19.5 (*E*), 19.4 (*Z*).

MS (ESI, MeOH): *m*/*z* = 292.9 ([M + Na]$^+$).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{10}N_6O_2Na$: 293.0763; found: 293.0749.

6-Methyl-3-(piperidin-1-ylmethylene)pyridine-2,4(1*H*,3*H*)-dione (4)

Following the typical procedure using **19** (1.31 mmol) and piperidine (1.44 mmol) in EtOH (4 mL) with stirring at 25 °C for 12 h gave **4** as a yellow solid as a single stereoisomer; yield: 0.19 g (65%); mp 250–252 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.64 (br s, 1 H), 8.21 (s, 1 H), 5.52 (s, 1 H), 3.93 (br s, 2 H), 3.70 (br s, 2 H), 2.10 (s, 3 H), 1.84 (br s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.0, 166.5, 161.3, 148.1, 107.8, 101.7, 59.2, 54.7, 27.0, 26.6, 23.4, 19.6.

MS (ESI, MeOH): *m*/*z* = 243.5 ([M + Na]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{17}N_2O_2$: 221.1290; found: 221.1262.

6-Methyl-3-(4-methylpiperazin-1-ylmethylene)pyridine-2,4(1*H*,3*H*)-dione (5)

Following the typical procedure using **19** (1.31 mmol) and 1-methylpiperazine (1.44 mmol) in EtOH (4 mL) with stirring at 25 °C for 12 h gave **5** as a yellow solid; yield: 0.29 g (93%); mp 216 °C (dec.).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.41 (br s, 1 H), 8.22 (s, 1 H), 5.53 (s, 1 H), 4.03–4.15 (m, 2 H), 3.71–3.82 (m, 2 H), 2.54–2.72 (m, 4 H), 2.35 (s, 3 H), 2.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.2, 161.2, 148.5, 107.9, 102.1, 100.0, 57.6, 55.4, 55.3, 53.6, 45.8, 19.7.

MS (ESI, MeOH): *m*/*z* = 258.4 ([M + Na]$^+$).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{17}N_3O_2Na$: 258.1218; found: 258.1242.

6-Methyl-3-(4-phenylpiperazin-1-ylmethylene)pyridine-2,4(1*H*,3*H*)-dione (6)

Following the typical procedure using **19** (1.31 mmol) and 1-phenylpiperazine (1.60 mmol) in EtOH (4 mL) with stirring at 25 °C for 12 h gave **6** as a yellow solid; yield: 0.29 g (75%); mp 201 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.01 (s, 1 H, NH), 8.22 (s, 1 H, =CH), 7.25 (t, *J* = 8 Hz, 2 H), 7.00 (d, *J* = 8 Hz, 2 H), 6.84 (t, *J* = 8 Hz, 1 H), 5.20 (s, 1 H, =CH), 4.12–4.09 (m, 2 H), 3.85–3.92 (m, 2 H), 3.42–3.35 (m, 4 H), 1.95 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 150.1, 148.4, 148.3, 129.0, 119.5, 115.9, 112.1, 106.1, 101.5, 56.0, 52.3, 49.1, 48.8, 18.8.

MS (ESI, MeOH): *m*/*z* = 320.2 ([M + Na]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}N_3O_2$: 298.1556; found: 298.1570.

6-Methyl-3-(morpholin-4-ylmethylene)pyridine-2,4(1*H*,3*H*)-dione (7)

Following the typical procedure using **19** (1.31 mmol) and morpholine (2.60 mmol) in EtOH (4 mL) with stirring at 25 °C for 24 h, and crystallization of the crude product (EtOAc–Et_2O, 1:1) gave **7** as a yellow solid; yield: 0.19 g (65%); mp 180–182 °C (dec.).

^{1}H NMR (400 MHz, $CDCl_3$): δ =8.71, (br s, 1 H), 8.23 (s, 1 H), 5.53 (s, 1 H), 4.26–3.56 (m, 8 H), 2.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 148.7, 130.2, 118.7, 107.8, 102.3, 67.4, 67.2, 57.6, 54.3, 19.7.

MS (ESI, MeOH): *m*/*z* = 223.2 ([M + H]$^+$).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{14}N_2O_3Na$: 245.0902; found: 245.0892.

7-Methyl-3-(phenylsulfinyl)-2*H*-pyrano[3,2-*c*]pyridine-2,5(6*H*)-dione (8); Typical Procedure for the Synthesis of Compounds 8–12

To a solution of **19** (0.16 mmol) and methyl α-(phenylsulfinyl)acetate (0.20 mmol) in anhyd EtOH (1 mL) under argon was added piperidine (0.01 mmol) and the mixture stirred at 80 °C for 48 h. The mixture was cooled to 25 °C and concentrated on a rotary evaporator to give a solid that was washed with Et_2O, suspended in CH_2Cl_2 (1 mL), and filtered. The resulting solid was washed with CH_2Cl_2 (2 ×) and dried under vacuum to give **8** as a yellow solid; yield: 34 mg (69%); mp 281–283 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.43 (s, 1 H), 8.36 (s, 1 H), 7.75–7.70 (m, 2 H), 7.52–7.50 (m, 3 H), 6.30 (s, 1 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.7, 160.1, 156.0, 153.0, 142.8, 137.4, 132.0, 129.5, 127.2, 125.6, 105.7, 96.7, 19.3.

MS (ESI, MeOH): *m*/*z* = 324.2 ([M + Na]$^+$).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{11}NO_4SNa$: 324.0307; found: 324.0305.

7-Methyl-3-(phenylsulfonyl)-2*H*-pyrano[3,2-*c*]pyridine-2,5(6*H*)-dione (9)

Following the typical procedure using **19** (0.20 mmol), methyl α-(phenylsulfonyl)acetate (0.235 mmol), and piperidine (0.01 mmol) in EtOH (1 mL) with stirring at 80 °C for 48 h gave **9** as a yellow solid; yield: 50 mg (81%); mp >300 °C (had not melted).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.41 (s, 1 H), 8.66 (s, 1 H), 8.00 (d, *J* = 7.5 Hz, 2 H), 7.70 (t, *J* = 7.5 Hz, 1 H), 7.60 (t, *J* = 7.5 Hz, 2 H), 6.33 (s, 1 H), 2.31 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.6, 160.8, 156.5, 155.1, 145.7, 139.5, 134.8, 129.9, 129.1, 121.6, 105.6, 97.5, 20.3.

MS (ESI, MeOH): *m*/*z* = 340.4 ([M + Na]$^+$).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{11}NO_5SNa$: 340.0256; found: 340.0246.

3-Benzoyl-7-methyl-2*H*-pyrano[3,2-*c*]pyridine-2,5(6*H*)-dione (10)

Following the typical procedure using **19** (0.65 mmol), ethyl 3-oxo-3-phenylpropanoate (0.98 mmol), and piperidine (0.03 mmol) in EtOH (3 mL) with stirring at 80 °C for 48 h gave **10** as a yellow solid; yield: 0.18 g (100%); mp 312–314 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.23 (br s, 1 H), 8.15 (s, 1 H), 7.84 (d, *J* = 7.5 Hz, 2 H), 7.66 (t, *J* = 7.5 Hz, 1 H), 7.53 (t, *J* = 7.5 Hz, 2 H), 6.33 (s, 1 H), 2.32 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 191.3, 165.6, 160.3, 157.5, 153.4, 143.6, 136.7, 133.3, 129.3, 128.5, 120.5, 105.2, 96.8, 19.4.

MS (ESI, MeOH): *m*/*z* = 304.1 ([M + Na]$^+$).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{11}NO_4Na$: 304.0586; found: 304.0586.

3-(2-Aminoacetyl)-7-methyl-2*H*-pyrano[3,2-*c*]pyridine-2,5(6*H*)-dione (11)

Following the typical procedure using **19** (0.99 mmol), ethyl 4-[(*tert*-butoxycarbonyl)amino]-3-oxobutanoate (**20**, 1.5 mmol),[10] and piperidine (0.05 mmol) in EtOH (3 mL) with stirring at 70 °C for 48 h, and column chromatographic purification (silica gel, CH_2Cl_2–MeOH, 15:1) gave **21** as a colorless oil; yield: 0.15 g (45%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.29 (s, 1 H), 8.50 (s, 1 H), 7.69–7.70 (br s, 1 H), 6.34 (s, 1 H), 4.32 (d, *J* = 5.9 Hz, 2 H), 2.32 (s, 3 H), 1.39 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 192.3, 166.4, 160.4, 158.3, 155.8, 155.0, 144.6, 117.1, 105.5, 96.7, 78.0, 49.8, 28.2, 19.5.

MS (ESI, MeOH): *m*/*z* = 357.3 ([M + Na]$^+$).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{18}N_2O_6Na$: 357.1057; found: 357.1066.

A solution of **21** (0.024 mmol) in 10% TFA–CH_2Cl_2 (1 mL) was stirred at 25 °C for 8 h. The solvent was removed in vacuo and the remaining solid kept under high vacuum to yield **11** as a yellow solid; yield: 8 mg (100%); mp 310 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.39 (br s, 1 H), 8.58 (s, 1 H), 8.10–8.20 (br s, 2 H), 6.35 (s, 1 H), 4.32 (s, 2 H), 2.30 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 187.9, 165.7, 159.2, 157.1, 155.1, 144.2, 114.5, 104.5, 95.7, 46.4, 18.5.

MS (ESI, MeOH): *m*/*z* = 235.2 ([M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{11}N_2O_4$: 235.0719; found: 235.0728.

Ethyl 4-{(*tert*-Butoxycarbonyl)[4-(*tert*-butoxycarbonyloxy)benzyl]amino}-3-oxobutanoate (22)

To a cold (0 °C) solution of 4-(aminomethyl)phenol (40.6 mmol) and Et_3N (40.6 mmol) in THF (50 mL) under argon was added methyl 2-bromoacetate (28.4 mmol) dropwise, and the solution was stirred at 25 °C for 12 h, concentrated, and column chromatographed (silica gel, CH_2Cl_2–MeOH, 9:1) to give methyl (4-hydroxybenzylamino)acetate[17] as an off-white solid; yield: 3.6 g (45%); mp 105–107 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.25 (br s, 1 H, OH), 8.30 (s, 1 H, NH), 7.10 (d, *J* = 7.5 Hz, 2 H), 6.70 (d, *J* = 7.5 Hz, 2 H), 3.60 (s, 3 H), 3.55 (s, 2 H), 3.24 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 155.4, 130.2, 129.8, 115.5, 52.7, 51.9, 49.5.

MS (ESI, MeOH): *m*/*z* = 218.1 ([M + Na]$^+$).

To a solution of methyl (4-hydroxybenzylamino)acetate (5.31 mmol) in 1,4-dioxane–H_2O (9:1, 5 mL), $NaHCO_3$ (11.6 mmol) was added and the mixture was stirred at 25 °C for 5 min. Boc_2O (11.6 mmol) was added to the mixture, and it was stirred for 12 h, diluted with brine (40 mL), and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic layers were washed with H_2O and brine, dried (anhyd Na_2SO_4), concentrated, and column chromatographed (silica gel, CH_2Cl_2–MeOH, 20:1) to give methyl [(*tert*-butoxycarbonyl)(4-hydroxybenzyl)amino]acetate as a colorless oil; yield: 1.19 g (76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (2 rotamers) = 7.07–7.05 (m, 2 H), 6.82–6.77 (m, 2 H), 6.47–6.45 (br s, 1 H), 4.45 / 4.42 (2 s, 2 H), 3.90 and 3.78 (2 s, 2 H), 3.71 and 3.68 (2 s, 3 H), 1.49 and 1.47 (2 s, 9 H).

MS (ESI, MeOH): *m*/*z* = 318.3 ([M + Na]$^+$).

To a solution of methyl [(*tert*-butoxycarbonyl)(4-hydroxybenzyl)amino]acetate (4.03 mmol) in 1,4-dioxane–H_2O (1:1, 2 mL), NaOH (12.1 mmol) was added. The solution was stirred at 25 °C for 2 h, neutralized with 1 M HCl to pH 6, and concentrated to dryness leaving a white solid. The solid was dissolved in anhyd DMF (5 mL) under argon, and NaH (8.11 mmol) and Boc_2O (4.87 mmol) were added. The solution was stirred at 25 °C for 12 h, diluted with H_2O, and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine, dried (anhyd Na_2SO_4), concentrated to give {(*tert*-butoxycarbonyl)[4-(*tert*-butoxycarbonyloxy)benzyl]amino}acetic acid as a colorless oil; yield: 1.56 g (84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (2 rotamers) = 7.28–7.22 (m, 2 H), 7.14–7.11 (m, 2 H), 4.53–4.49 (m, 2 H), 3.94–3.80 (m, 2 H), 1.55–1.52 (m, 9 H), 1.48–1.47 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (2 rotamers) = 174.58, 174.57, 155.5, 155.4, 151.6, 150.3, 134.5, 134.4, 128.9, 128.2, 121.2, 83.3, 81.0, 80.8, 50.8, 50.2, 47.5, 28.1, 28.0, 27.4.

MS (ESI, MeOH; negative ion mode): *m*/*z* = 380.5 ([M – H]$^-$).

To a solution of {(*tert*-butoxycarbonyl)[4-(*tert*-butoxycarbonyloxy)benzyl]amino}acetic acid (4.09 mmol) in anhyd THF (4 mL) under argon was added CDI (4.44 mmol). The solution was stirred at 25 °C for 4 h to give the corresponding acylimidazole. To a mixture of $MgCl_2$ (0.54 g, 5.65 mmol) and monoethyl malonate potassium salt (0.71 g, 5.36 mmol) under argon, Et_3N (0.85 mL, 6.14 mmol) and THF (2 mL) were added. The solution was stirred at 25 °C for 4 h, and the above acylimidazole solution was added via cannula. The resulting mixture was stirred at 25 °C for 18 h, diluted with H_2O and 0.1 M HCl to pH 5, and extracted with EtOAc (3 ×). The combined organic layers were washed with aq $NaHCO_3$, and brine, dried (anhyd Na_2SO_4), concentrated, and column chromatographed (silica gel, hexane–EtOAc, 15:1) to give **22** as a colorless oil; yield: 0.66 g (36%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (2 rotamers) = 7.28–7.20 (m, 2 H), 7.14–7.12 (m, 2 H), 4.49–4.45 (m, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.07 and 3.93 (2 s, 2 H, 2 rotamers), 3.42 and 3.35 (2 s, 2 H, 2 rotamers), 1.56 (s, 9 H), 1.47 (s, 9 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (2 rotamers) = 198.8, 198.6, 166.8, 166.6, 155.6, 155.3, 151.8, 150.5, 150.4, 134.9, 134.8, 129.2, 128.5, 121.4, 83.6, 80.9, 61.5, 55.8, 55.4, 51.0, 50.5, 46.4, 46.2, 28.3, 28.1, 27.64, 27.59, 14.0.

MS (ESI, MeOH): *m*/*z* = 474.5 ($[M + Na]^+$).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{33}NO_8Na$: 474.2098; found: 474.2087.

3-[2-(4-Hydroxybenzylamino)acetyl]-7-methyl-2*H*-pyrano[3,2-*c*]pyridine-2,5(6*H*)-dione (12)

To a solution of **19** (1.22 mmol) and **22** (1.22 mmol) in EtOH (8 mL) under argon was added piperidine (0.05 mmol), and the mixture was stirred at 70 °C for 48 h. It was cooled to 25 °C, diluted with Et_2O (10 mL), and the solid was collected by filtration and purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 15:1) to give the *N*-Boc derivative of **12** as a yellow solid; yield: 0.26 g (41%); mp 188–190 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (2 rotamers) = 12.87 and 12.80 (2 br s, 1 H, NH for 2 rotamers), 8.85 and 8.83 (2 s, 1 H, =CH), 7.27–7.25 (m, 2 H, Ar), 7.13–7.09 (m, 2 H, Ar), 6.16 and 6.14 (2 s, 1 H, =CH), 4.62 (s, 1 H, CH_2N of 1 rotamer), 4.53 (br s, 2 H, CH_2N), 4.50 (s, 1 H, CH_2N of 1 rotamer), 2.47 and 2.45 (2 s, 3 H, 2 rotamers), 1.54 and 1.53 (2 s, 9 H, *t*-Bu, 2 rotamers), 1.45 and 1.41 (2 s, 9 H, 2 rotamers).

^{13}C NMR (100 MHz, $CDCl_3$): δ (2 rotamers) = 191.7, 191.6, 166.7, 162.6, 158.2, 155.8, 153.6, 153.5, 151.8, 150.2, 145.6, 135.4, 135.2, 128.9, 128.3, 121.2, 118.5, 118.3, 105.8, 98.3, 83.5, 80.5, 80.2, 56.3, 56.2, 51.5, 50.6, 28.3, 28.2, 27.6, 20.0.

MS (ESI, MeOH): *m*/*z* = 563.7 ($[M + Na]^+$).

The above solid (0.10 mmol) was dissolved in 20% TFA–CH_2Cl_2 (1 mL) and stirred at 25 °C for 30 min. The solvent was removed under a rotary evaporator and the remaining solid was kept under high vacuum to yield compound **12**·TFA as a yellow solid; yield: 34 mg (100% yield); mp 180–181 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.42 (br s, 1 H), 9.69 (br s, 1 H), 9.15 (br s, 1 H), 8.61 (s, 1 H), 7.31 (d, *J* = 8.6 Hz, 2 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 6.40 (s, 1 H), 4.46 (s, 2 H), 4.10 (s, 2 H), 2.34 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.3, 169.5, 165.0, 158.2, 157.0, 154.1, 137.3, 129.6, 121.5, 115.5, 114.5, 105.5, 96.9, 53.7, 45.6, 18.9.

MS (ESI, MeOH): *m*/*z* = 341.4 ($[M + H]^+$).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{16}N_2O_5Na$: 363.0957; found: 363.0981.

3-Amino-4-hydroxy-6-methyl-2*H*-pyran-2-one (23)[13]

To a cold (0 °C) solution of 4-hydroxy-6-methyl-2*H*-pyran-2-one (79.3 mmol) in H_2SO_4 (25 mL) was added dropwise a mixture of H_2SO_4 (4.23 mL) and HNO_3 (119 mmol) over 10 min. After stirring for 30 min, the mixture was poured into ice-water, and the precipitate was collected by filtration, washed with cold H_2O (3 ×) and dried under vacuum to give 4-hydroxy-6-methyl-3-nitro-2*H*-pyran-2-one as a white solid; yield: 10.7 g (79%); mp 163–166 °C (Lit.[18] 165 °C).

IR (solid form): 1748, 1639, 1530, 1215, 1194, 1086, 996, 827, 783 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.21 (br s, 1 H, OH), 6.14 (s, 1 H, =CH), 2.37 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.4, 165.4, 156.6, 119.5, 100.7, 19.8.

MS (ESI, MeOH, negative ion mode): *m*/*z* = 170.4 ($[M - H]^-$).

A solution of 4-hydroxy-6-methyl-3-nitro-2*H*-pyran-2-one (2.0 g, 11.7 mmol) and 10% Pd/C (0.2 g) in MeOH (30 mL) was stirred under 1 atm of H_2 at 25 °C for 18 h. The mixture was filtered and concentrated to give **23**[13] as a brown solid; yield: 1.33 g (80%); mp 198–200 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.31 (s, 1 H, =CH), 3.80 (br s, 3 H, NH_2, OH), 2.22 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.7, 153.5, 119.6, 104.4, 103.3, 18.9.

MS (ESI, MeOH): *m*/*z* = 164.1 ($[M + Na]^+$).

***tert*-Butyl (4-Hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)carbamate (24)**

To a hot (85 °C) solution of 3-amino-4-hydroxy-6-methyl-2*H*-pyran-2-one (**23**, 1.28 mmol) in MeCN (5 mL) under argon was added Boc_2O (2.46 mmol) in portionwise over a period of 6 h. The solution was cooled and concentrated on a rotary evaporator to give an oil, which was purified by flash chromatography (silica gel, hexane–EtOAc, gradient elution) to yield **24** as a white solid; yield: 0.18 g (57%); mp 87–89 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.08 (s, 1 H, OH), 7.05 (s, 1 H, NH), 5.88 (s, 1 H, =CH), 2.21 (s, 3 H, CH_3), 1.50 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 156.7, 156.6, 155.1, 103.6, 102.8, 83.7, 28.2, 19.4.

MS (ESI, MeOH): *m*/*z* = 264.0 ($[M + Na]^+$).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{15}NO_5Na$: 264.0848; found: 264.0831.

***tert*-Butyl (8a*S**,10a*R**)-3-Methyl-1-oxo-5,8a,9,10a-tetrahydro-1*H*,6*H*-2,10-dioxa-9-azaanthracene-9-carboxylate (27)**

To a cold (0 °C) mixture of NaH (0.25 mmol) in anhyd DMF (1 mL) under argon was added **24** (0.25 mmol), and the mixture was stirred at 25 °C for 30 min. The solution was again cooled to 0 °C and a solution of *trans*-3,6-dibromocyclohexene (**25**, 0.3 mmol) in anhyd DMF (1 mL) was added via cannula, and the mixture was stirred at 25 °C for 18 h. To the mixture were added anhyd MeCN (10 mL) and Et_3N (0.25 mmol), and the solution was heated at 95 °C for 8 h. The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (50 mL), and the organic layer was washed with brine (20 mL), dried ($MgSO_4$), concentrated, and column chromatographed (silica gel, hexane–EtOAc, 1:1) to give **27** as a white solid; yield: 20 mg (25%); mp 129–130 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78–5.71 (m, 1 H, C8H), 5.72 (s, 1 H, C4H), 5.35–5.25 (m, 1 H, C7H), 5.05–4.9 (m, 1 H, C8aH), 4.55–4.50 (m, 1 H C10aH), 2.25–1.85 (m, 4 H), 2.19 (s, 3 H, CH_3), 1.50 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 159.1, 157.3, 153.4, 131.6, 123.9, 102.5, 99.4, 82.2, 74.5, 48.6, 28.4, 25.9, 19.9, 19.5.

2D-COSY NMR (acetone-d_6, the use of acetone-d_6 as a solvent has changed the chemical shifts slightly from that of $CDCl_3$): signal C10aH (δ = 4.57) correlates with signal C8aH (δ = 5.04), signal C8aH (δ = 5.04) correlates with signal C8H (δ = 5.78–5.71), and signal C8H correlates with signal C7H (δ = 5.29).

MS (ESI, MeOH): m/z = 342.3 ($[M + Na]^+$).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{17}H_{21}NO_5Na$: 342.1317; found: 342.1299.

(8a*S,10a*R**)-3-Methyl-5,8a,9,10a-tetrahydro-1*H*,6*H*-2,10-dioxa-9-azaanthracen-1-one (13)**

A solution of **27** (0.04 mmol) in CH_2Cl_2 containing 10% TFA was stirred at 40 °C for 1 h. The solution was diluted with H_2O (20 mL), basified with 10% aq NH_4OH, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed (silica gel, EtOAc–hexane, 1:1) to give **13** as a white solid; yield: 9 mg (100%); mp 131–133 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.86–5.80 (m, 1 H, =CH), 5.82 (s, 1 H, =CH), 5.53–5.50 (m, 1 H, CH=), 4.48–4.40 (m, 1 H, CHO), 3.87 (s, 1 H, CHN), 3.78 (br s, 1 H, NH), 2.06–2.34 (m, 3 H, CH_2CH_2), 2.17 (s, 3 H, CH_3), 1.91–1.81 (m, 1 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.9, 152.0, 148.3, 130.7, 126.7, 110.3, 100.6, 73.3, 47.4, 25.7, 22.1, 19.5.

MS (ESI, MeOH): m/z = 242.5 ($[M + H]^+$).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{12}H_{13}NO_3Na$: 242.0793; found: 242.0775.

***tert*-Butyl (8*R**,8a*S**,10a*R**)-8-Hydroxy-3-methyl-1-oxo-5,7,8,8a,9,10a-hexahydro-1*H*,6*H*-2,10-dioxa-9-azaanthracene-9-carboxylate (28)**

To a solution of **27** (0.11 mmol) in anhyd THF (0.5 mL) at 0 °C under argon was added 1 M BH_3·THF in THF (0.109 mmol) and the resulting solution was stirred at 25 °C for 18 h, cooled to 0 °C, and 30% H_2O_2 (1 mL) and 0.1% aq NaOH (1 mL) were added. The mixture was stirred for 10 min at 0 °C followed by 3 h at 25 °C, diluted with H_2O, and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed (silica gel, hexane–EtOAc, gradient) to give **28** as a white solid; yield: 32 mg (87%); mp 162–163 °C; TLC and NMR spectral data indicate it to be a single stereoisomer and 2D COSY and NOESY spectra show the hydroxy function is *cis* to the angular hydrogens (C8aH and C10aH).

^1H NMR (400 MHz, $CDCl_3$): δ = 5.82 (s, 1 H, C4H), 4.40 (q, J = 3.5 Hz, 1 H, C10aH), 4.22 (dd, J = 10.1, 3.5 Hz, 1 H, C8aH), 3.33 (td, J = 10.5, 3.5 Hz, 1 H, C8H), 2.90 (br s, 1 H, OH), 2.23 (s, 3 H), 2.18–2.06 (m, 2 H), 1.72–1.63 (m, 2 H), 1.50 (s, 9 H), 1.50–1.38 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 159.1, 156.0, 153.9, 102.9, 99.4, 82.8, 76.6, 65.5, 57.4, 32.2, 29.9, 28.2, 19.9, 18.4.

2D-NOESY NMR (400 MHz, $CDCl_3$): signal C4H (δ = 5.82) correlates with signal C3-Me (δ = 2.23), signal C10aH (δ = 4.40) correlates with signal C8aH (δ = 4.22), and signal C8aH (δ = 4.22) correlates with signal C8H (δ = 3.33). No correlation is found between signals C8H and C10aH.

MS (ESI, MeOH): m/z = 360.5 ($[M + Na]^+$).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{17}H_{23}NO_6Na$: 360.1423; found: 360.1411.

(8*R,8a*S**,10a*R**)-8-Hydroxy-3-methyl-5,7,8,8a,9,10a-hexahydro-1*H*,6*H*-2,10-dioxa-9-azaanthracen-1-one (14)**

A solution of **28** (0.065 mmol) in 10% TFA (2 mL) in CH_2Cl_2 was stirred at 40 °C for 1 h, partitioned between CH_2Cl_2 (10 mL) and H_2O (20 mL), and basified using 10% aq NH_4OH. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated on a rotary evaporator to give a solid that was purified by column chromatography (silica gel, EtOAc–hexane, 8:1) to afford **14** as a white solid; yield: 10 mg (65%); mp 92–94 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.81 (s, 1 H), 4.33 (s, 1 H), 4.15 (br s, 1 H), 3.60–3.54 (m, 1 H), 3.21–3.19 (m, 1 H), 2.19 (s, 3 H), 2.18–2.02 (m, 4 H), 1.43–1.32 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 152.1, 148.7, 110.7, 100.7, 74.5, 67.6, 57.4, 32.6, 29.9, 19.4, 18.8.

MS (ESI, MeOH): m/z = 260.3 ($[M + Na]^+$).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{12}H_{15}NO_4Na$: 260.0899; found: 260.0884.

***tert*-Butyl (8a*R**,10a*R**)-3-Methyl-1,8-dioxo-5,7,8,8a,9,10a-hexahydro-1*H*,6*H*-2,10-dioxa-9-azaanthracene-9-carboxylate (15)**

To a solution of **28** (0.024 mmol) in DMSO (0.5 mL) under argon was added 2-iodoxybenzoic acid (IBX, 0.034 mmol), and the solution was stirred at 25 °C for 2 h. Additional IBX (0.034 mmol) was added and the mixture was stirred for 12 h after which the mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give **15** as a white solid; yield: 7 mg (87%); mp 90–92 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.69 (s, 1 H, C4H), 5.20 (d, J = 4 Hz, 1 H, C8aH), 4.75 (q, J = 4 Hz, 1 H, C10aH), 2.54–1.85 (m, 6 H), 2.17 (s, 3 H), 1.50 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 159.4, 158.8, 155.0, 152.4, 104.5, 98.9, 83.2, 79.7, 60.4, 41.3, 29.5, 28.2, 21.6, 19.8.

MS (ESI, MeOH): m/z = 358.3 ($[M + Na]^+$).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{17}H_{21}NO_6Na$: 358.1267; found: 358.1257.

4-Hydroxy-3-(4-methoxybenzylamino)-6-methyl-2*H*-pyran-2-one (29)

A solution of **23** (1.42 mmol) and *p*-anisaldehyde (1.42 mmol) in MeOH (10 mL) was stirred at 25 °C for 12 h. The solution was concentrated to give intermediate compound 4-hydroxy-3-(4-methoxybenzylideneamino)-6-methyl-2*H*-pyran-2-one (0.37 g, 100%) as a yellow solid, which was used for the next step without further purification. To a solution the aforementioned imine (1.04 mmol) in EtOH (15 mL) was added $NaCNBH_3$ (1.25 mmol) and AcOH (1.25 mmol) at 25 °C. The solution was stirred for 30 min and then it was diluted with aq $NaHCO_3$ (1.5 mmol) and concentrated to give a crude oil that was purified by column chromatography (silica gel, 5% MeOH–CH_2Cl_2) to give **29** as a yellow solid; yield: 0.24 g (89%); mp 179–181 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.80 (br s, 2 H, NH, OH), 7.25 (d, J = 8.8 Hz, 2 H, Ar-H), 6.84 (d, J = 8.8 Hz, 2 H, Ar-H), 5.61 (s, 1 H, =CH), 4.17 (s, 2 H, CH_2N), 3.71 (s, 3 H, OCH_3), 2.00 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.8, 161.6, 158.9, 156.8, 130.6, 127.1, 113.5, 104.9, 101.5, 55.0, 48.7, 19.1.

MS (ESI, MeOH): m/z = 284.2 ($[M + Na]^+$).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{14}H_{15}NO_4Na$: 284.0899; found: 284.0895.

(8a*S,10a*R**)-9-(4-Methoxybenzyl)-3-methyl-7,8,8a,10a-tetrahydro-1*H*,9*H*-2,10-dioxa-9-azaanthracen-1-one (30)**

A solution of **29** (20 mg, 76 μmol), *trans*-3,6-dibromocyclohexene (**25**, 31 mg, 0.13 mmol), and Et_3N (39 μL, 0.28 mmol) in DMF (1 mL) was stirred at 80 °C under argon for 2.5 h. The mixture was diluted with EtOAc (50 mL) and washed with H_2O (3 × 10 mL), and brine, dried ($MgSO_4$), concentrated, and column chromatographed (silica gel, 30% EtOAc–hexane) to give **30** as a pale yellow solid; yield: 13 mg (50%); mp 300 °C (had not melted).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.0 Hz, 2 H, Ar-H), 6.86 (d, *J* = 8.0 Hz, 2 H, Ar-H), 6.04–5.97 (m, 1 H, CH=), 5.96–5.90 (m, 1 H, CH=), 5.78 (s, 1 H, CH=), 4.49 (d, *J* = 12 Hz, 1 H, Ar-CH_2N), 4.01 (d, *J* = 12 Hz, 1 H, Ar-CH_2N), 3.87 (t, *J* = 4 Hz, 1 H, CHO), 3.81 (s, 3 H, Ar-OCH_3), 3.02 (dt, *J* = 12, 4 Hz, 1 H, CHN), 2.21 (s, 3 H, CH_3), 2.18–2.03 (m, 2 H, CH_2), 1.52–1.32 (m, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 159.1, 155.0, 152.4, 135.5, 130.5, 130.4, 123.8, 113.9, 111.1, 100.4, 66.3, 56.5, 55.4, 53.4, 26.4, 22.6, 19.6.

2D COSY NMR (400 MHz, $CDCl_3$): signal (δ = 6.04–5.97; =CH) correlates with signal (δ = 5.96–5.90; =CH), signal (δ = 6.04–5.97; =CH) correlates with signal (δ = 2.18–2.03), signal (δ = 2.18–2.03) correlates with signal (δ = 1.52–1.32), signal (δ = 1.52–1.32) correlates with signal (δ = 3.02, C8aH), and signal (δ = 3.02=) correlates with signal (δ = 3.87, C10aH).

MS (ESI, MeOH): *m*/*z* = 362.2 ([M + Na]$^+$).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{21}NO_4Na$: 362.1368; found: 362.1360.

(8a*S,10a*R**)-3-Methyl-7,8,8a,10a-tetrahydro-1*H*,9*H*-2,10-dioxa-9-azaanthracen-1-one (16)**

A solution of **30** (17.7 μmol) and TFA (1 drop) in CH_2Cl_2 (1 mL) was heated at refluxed for 12 h under argon, cooled to 25 °C, diluted with sat. aq $NaHCO_3$, and extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed (silica gel, 20% EtOAc–hexane) to afford **16** as a white solid; yield: 2.3 mg (59%); mp 134–136 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.97 (dt, *J* = 10.0, 3.6 Hz, 1 H, CH=), 5.82 (s, 1 H, =CH), 5.81–5.70 (m, 1 H, CH=), 4.61 (s, 1 H, CHO), 3.76 (s, 1 H, NH), 3.63–3.50 (m, 1 H, CHN), 2.40–2.27 (m, 1 H, CH_2), 2.18 (s, 3 H, CH_3), 2.18–2.10 (m, 1 H, CH_2), 1.94–1.68 (m, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 151.1, 145.7, 133.3, 124.4, 111.8, 100.7, 71.3, 47.5, 25.4, 23.5, 19.3.

MS (ESI, MeOH): *m*/*z* = 242.6 ([M + Na]$^+$).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{13}NO_3Na$: 242.0793; found: 242.0776.

(8a*S,10a*R**)-3-Methyl-7,8,8a,10a-tetrahydro-1*H*,9*H*-2,10-dioxa-9-azaanthracen-1-one (16); One-Step Method**

A solution of **23** (3.54 mmol), *trans*-3,6-dibromocyclohexene (**25**, 4.25 mmol), and Et_3N (8.85 mmol) in DMF (35 mL) was stirred at 120 °C under argon for 2 h, cooled to 25 °C, diluted with sat. aq $NaHCO_3$, and extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried ($MgSO_4$), concentrated, and column chromatographed (silica gel, 10% EtOAc–hexane) to give **16** as a white solid; yield: 99 mg (13%).

The spectral data are identical to those described in the previous experiment. Slow evaporation of a solution of **16** in EtOH provided single crystals which were used for X-ray crystal structure analysis.

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