Photocycloaddition of Four-Carbon-Tethered Pyridones. Intramolecular Hydrogen Bonding and Facilitated Amide Hydrolysis by a Proximal Secondary Alcohol[1]

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Four-carbon-tethered pyridones undergo photocycloaddition to give exclusively trans-[4 + 4] products. The presence of a tether alcohol engenders a solvent-dependent diastereoselectivity for the cycloaddition by intramolecular hydrogen bonding to the adjacent pyridone. Following cycloaddition, the alcohol can deliver a carbonyl group to the proximal, hindered amide nitrogen, leading to a very facile amide hydrolysis.

Functional groups often play an important role as stereocontrol elements and as points of leverage for otherwise difficult reactivity. The intimate proximity of functional groups in 2-pyridone photodimers makes this interplay an important aspect of their chemistry. Our studies of intramolecular 2-pyridone photocycloadditions revealed that chirality on the tether can exert stereocontrol; hydrogen bonding by an alcohol to an adjacent pyridone carbonyl can bias the product distribution in favor of one diastereomer, whereas protection of the alcohol as a *tert*-butyldimethylsilyl ether leads to another diastereomer exclusively.[3−5] Most of these findings were in the context of three-carbon tethered pyridones. We describe here new followup studies of the synthesis and photocycloaddition of the four-carbon-tethered bis-2-pyridone **2** and a remarkably facile hydrolysis of the secondary amide of **1** mediated stereospecifically by the adjacent hydroxyl.

Photosubstrate Preparation. We reported the cycloaddition of **2** to give **1** in 1991, Figure 1.[6] Product **1** was identified as a mixture of two isomers differing only in the alcohol stereochemistry, but their identity was not verified.[6] To clear up this point as well as to investigate the subsequent chemistry of **1**, we required additional material; however, the original synthesis of **2** from **3** involved several difficult steps and intermediates such as **4** that were not readily available. We therefore began our reinvestigation exploring alternative synthetic routes to **2** via **6**, which in turn could be obtained from either **7** or **8**.

Quinoline **7** contains all of the carbons of **6** except the *N*-methyl group, and conversion of **7** to **6** could take advantage of Weber's investigations of the Decker oxidation.[7,8] Hydrogenation of **7** under acidic conditions preserves the pyridine ring to yield 5,6,7,8-tetrahydroquinoline in moderate yield, Scheme 1.[9−11] Treatment of this product with iodomethane cleanly and quantitatively gave methiodide **9**[7] and set the stage for Decker oxidation. Weber had shown that treatment of **9** with basic potassium ferricyanide led to oxidative cleavage of the saturated ring with concomitant formation of a pyridone carboxylic acid. This sequence generates one of the pyridone rings and all the carbons of the tether in only three steps. Fischer esterification and reduction of the ester with DIBAL gave conversion to alcohol **10** in high yield. While this sequence provided gram quantities of **10**, the overall yield was below 20%, prompting consideration of alternative approaches.

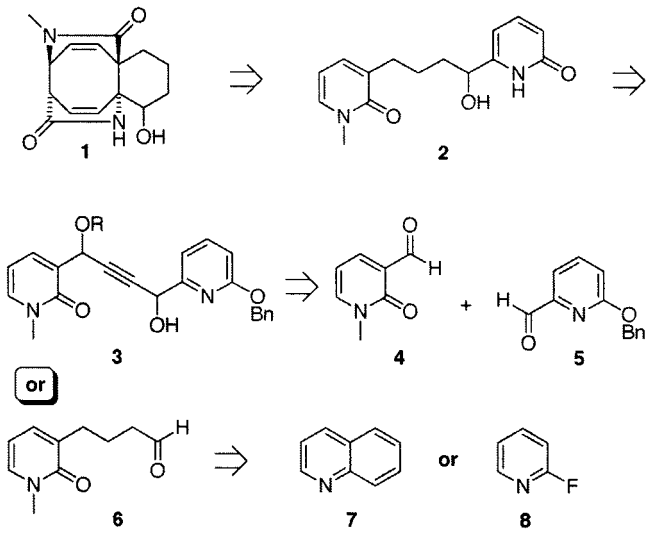

Figure 1. Intramolecular photoproduct **1** and its precursor **2**, which can be prepared from **3** or **6**.

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(1) Taken, in part, from: Zhu, M. M. S. Ph.D. Dissertation, SUNY Stony Brook, 1999; Qiu, Z. M. S. Ph.D. Dissertation, SUNY Stony Brook, 1998; Hiel, G. P. Ph.D. Dissertation, SUNY Stony Brook, 1997.

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(11) The intermediate 5,6,7,8-tetrahydroquinoline was intermittently available commercially during this investigation.

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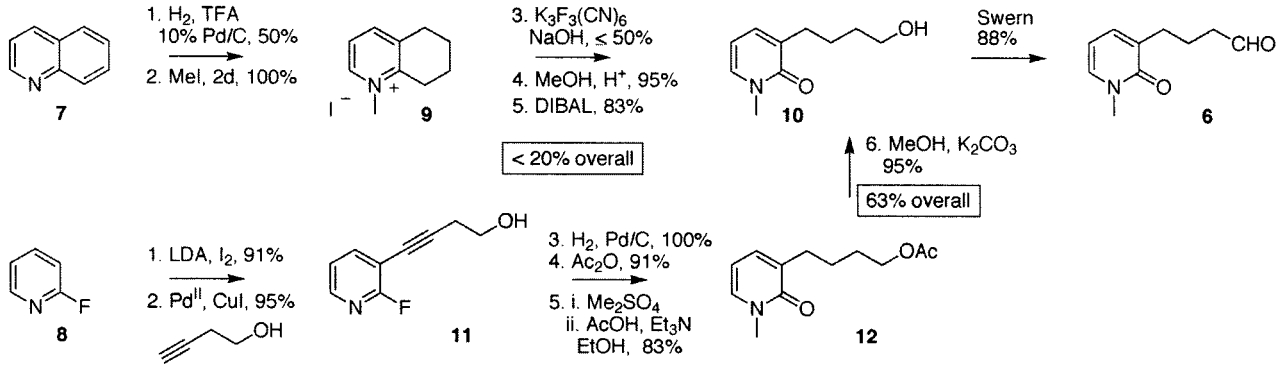
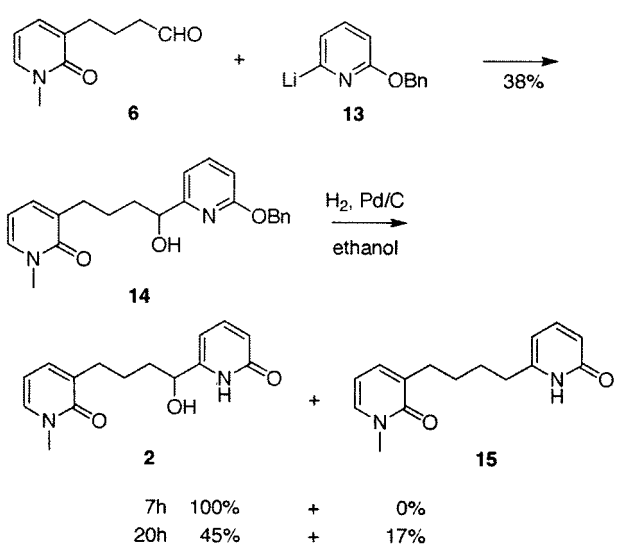
Scheme 1. Synthesis of Intermediate 6



Scheme 2. Coupling of 6 with Lithium Reagent 13



A more efficient alternative synthetic strategy began with commercially available 2-fluoropyridine **8**. Deprotonation of **8** with LDA and iodination to give 2-fluoro-3-iodopyridine had been reported by Quéguiner,[12] and this reaction proved to be reproducibly high yielding. Sonogashira coupling[13] of this iodide with 3-butyne-1-ol provided **11** in excellent yield. Saturation of the acetylene and acetylation of the alcohol set the stage for hydrolysis of the fluoropyridone. This was accomplished by N-methylation with dimethyl sulfate, followed by treatment with ethanolic triethylammonium acetate. Methanolysis of ester **12** then gave alcohol **10**. Preparation of **10** from **8** required six steps compared with five steps from quinoline **7**, but the overall yield from **8** was more than triple that from **7**. Introduction of the second pyridone of **1** was anticipated by Swern oxidation of **10** to aldehyde **6**.

The second pyridone was introduced using lithium reagent **13** to give **14**, albeit in modest yield, Scheme 2. Hydrogenolysis of **14** with palladium-on-carbon gave the desired alcohol **2** quantitatively. Extending the hydrogenation time was found to give a substantial proportion of deoxygenated **15**. While this reaction was not optimized for production of **15**, the availability of this photosubstrate was useful for defining the inherent stereoselectivity of the parent four-carbon photocycloaddition.

Photochemistry. 2-Pyridone photodimers are strained polycyclic products,[14] and when the photocycloaddition is intramolecular with a four-carbon tether, the [4 + 4] products have an additional portion of strain; the tether-derived six-membered ring fused to the rigid polycyclic pyridone dimer framework adopts a boat conformation as its lowest energy option.[15,16] In some cases, the strain can be great enough that the photoproducts decompose on silica gel chromatography. The photoreactions described here, using a Pyrex-filtered medium-pressure mercury lamp, were best run near 0 °C, and the yields of chromatographically isolated photoproducts were generally moderate. Under these photochemical conditions, only [4 + 4] products were formed in any significant amounts, as determined by ^{1}H NMR spectroscopy of the crude photoreaction mixture. The ratio of the isolated products paralleled the NMR-determined ratios.

Achiral **15** has the potential to form two diastereomeric [4 + 4] products (cis and trans), but underwent photocycloaddition to give only trans **16**, Scheme 3. The ^{1}H NMR spectrum of photoproduct **16** has a characteristic set of signals for the six protons surrounding the cyclooctadiene ring; the sequence of coupling is readily followed in the COSY spectrum (see Supporting Information). Also characteristic of the trans isomers is the dispersion of the alkene proton signals, presumably due to their proximity to amide groups (see Figure 2). Cis isomers are generally more labile than trans isomers and either are not formed or undergo Cope rearrangement/photofragmentation at the temperatures studied, behavior defined for less strained congeners.[17] Earlier studies[6,18] are consistent with these results; only trans pyridone photoproducts have been isolated from reactions of four-carbon-tethered pyridones. Hydrogenation of **16** gave the saturated polycyclic product **17**.

In agreement with our earlier report,[6] photoreaction of **2** gave products **1a** and **1b**, each of which could be isolated and hydrogenated to give **18** and **19**. The diastereoselectivity of the photocycloaddition was influenced by solvent. The two isomers are formed in nearly

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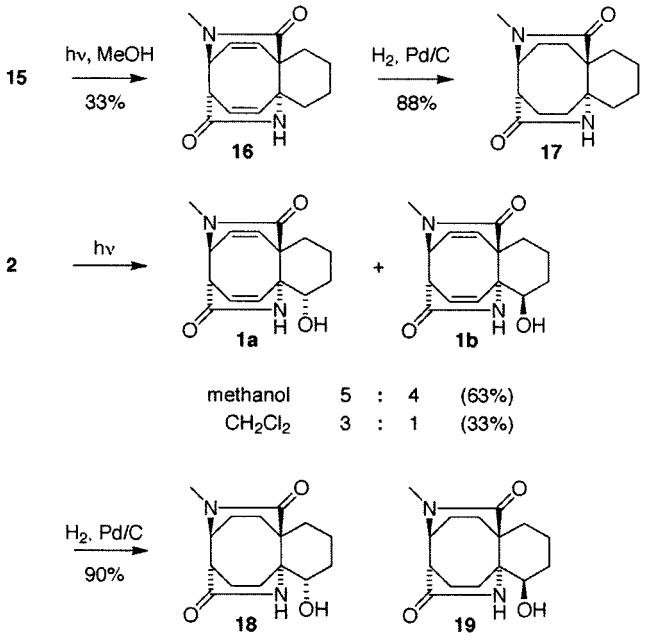
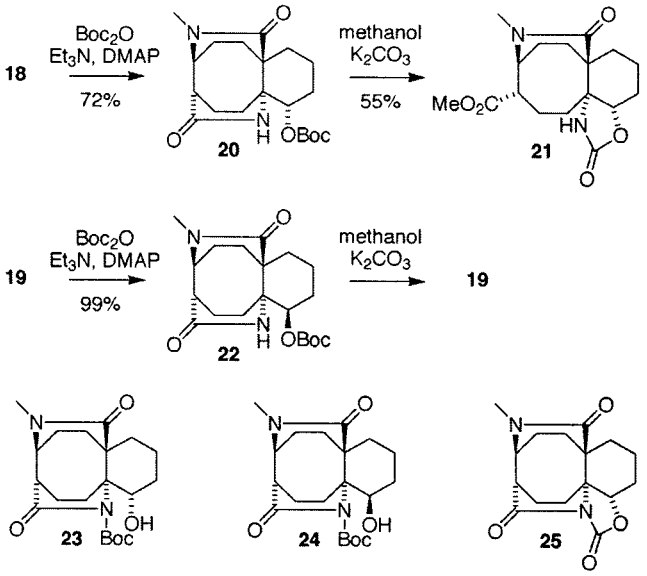
Scheme 3. Photocycloaddition of 15 and 2



Scheme 4. Boc-Derivatization of Alcohols 18 and 19, Followed by Methanolysis



equal amounts, slightly favoring **1a**, when methanol is the photochemistry solvent. When the solvent is changed to methylene chloride, isomer **1a** comprises three-fourths of the mixture. The product ratios shown in Scheme 3 were determined by NMR spectroscopy of the crude photoreaction mixture, and the indicated yields are for isolated products. The lower isolated yield for the methylene chloride reaction may reflect the effect of solvent photodecomposition.[19]

The solvent effect, while relatively small, is consistent with hydrogen bonding between the alcohol and the adjacent amide nitrogen. Changing the solvent from methylene chloride, where intramolecular hydrogen bonding would be promoted, to methanol, would attenuate intramolecular hydrogen bonding. Two photocycloaddition-conducive conformations of **2**, **2-A** and **2-B** both leading to **1a**, are shown in Figure 2. These structures differ in the half-chair conformation of the tether and were generated by holding C3 and C6 atoms of the pyridones within 3.5 Å while minimizing the tether conformations (Chem3D). Conformation **2-B** is capable of being stabilized by hydrogen bonding from the amide nitrogen to the alcohol. Following cycloaddition, the new tether-derived cyclohexane ring of trans-syn product **1a** can have the cyclohexane in either of two boat conformations, with **1a-B** calculated to be lower in energy relative to **1a-A** by 1.2 kcal/mol (Chem3D). The crystal structure of **18**[20] was found to be similar to the calculated structure of **1a-B**.

Amide Hydrolysis. Greico's Boc-activation method provides a very effective approach to secondary amide hydrolysis;[21] however, application of this procedure to pyridone photoproducts has given mixed results. In cases where the secondary amide nitrogen of the photoproducts was relatively unhindered, N-derivatization and hydrolysis occurred smoothly;[22] however, when the carbon attached to the secondary amide nitrogen was fully substituted, introduction of an activating group proved to be difficult, and Boc group introduction was fully unsuccessful.[23]

For **18** and **19** the secondary amide nitrogen is quite hindered. Nevertheless, treatment with di-*tert*-butyl dicarbonate led, in each case, to a Boc derivative. Moreover, dissolving these derivatives in methanol containing potassium carbonate resulted, in both cases, in loss of the *tert*-butyl group. For one of the isomers (**22**), the methanolysis returned only the starting **19**. For the other Boc derivative (**20**), loss of the *tert*-butyl group was accompanied by the appearance of a methyl ester. While appearance of the methyl ester was not unexpected, loss of the *tert*-butyl group was unexpected and suggested participation of the nearby alcohol. The most likely structure for this product was oxazolidinone **21**. The IR and ^{13}C NMR data were fully consistent with this structure, and the exact mass confirmed the identity.

A reasonable sequence of events leading to **21** is derivatization of the alcohols of **18** and **19** to give **20** and **22**, not the amide derivatives **23** and **24**. Coupling of a Boc group with the amide of a pyridone photoadduct in an earlier study resulted in an upfield shift of the carbonyl carbon in the ^{13}C NMR spectrum by about 4 ppm,[22] but an analogous change in the ^{13}C NMR spectra of **20** or **22** was not found. Hydrolysis of the amide in **20** must involve intramolecular delivery of the Boc group to the amide nitrogen. It seems likely that this would transiently result in intermediate **25**. It is notable that delivery of the Boc group by the alcohol requires that the cyclohexane ring (see Figure 2) adopt the higher-energy boat conformation with the Boc group in the flagpole position. While this is clearly an energetically unfavorable option, a similar conformation has been observed

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(20) Compound **18** crystallized in the monoclinic space group $P2_1/n$ with $a = 6.743$ (1) Å, $b = 16.645$ (2) Å, $c = 12.046$ (3) Å, $b = 102.87$ (2)°, $V = 1318.0$ (5) Å^3. The final least squares refinement using 882 unique reflections with $I > 3s(I)$ gave $R(R_w) = 0.055$ (0.044).

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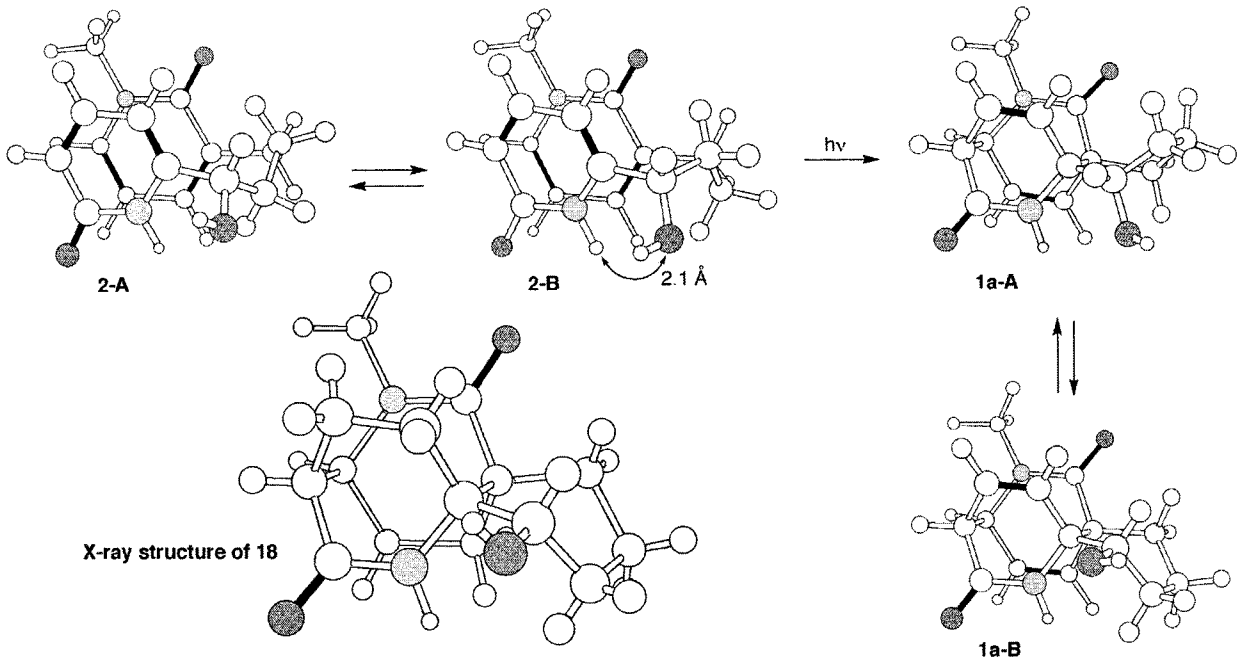

Figure 2. Molecular models of **2**, illustrating the potential for the alcohol to hydrogen bond to the amide nitrogen with the tether in a half-chairlike conformation, leading to trans,syn product **1a**. Pro-trans,anti conformational options are similar but are not shown. Following cycloaddition, the tether-derived cyclohexane preferentially adopts a boat conformation, with **1a-A** higher in energy than **1a-B**. A crystal structure of tetrahydro-**1a** (**18**) shows a conformation similar to that of calculated structure **1a-B**.

for a *tert*-butyldimethylsilyl ether in crystal structures of related molecules.[18,24]

The reaction of secondary alcohols with di-*tert*-butyl dicarbonate to form mixed carbonates is well precedented in the work of Fréchet[25] and more recently that of Hassner.[26] Nevertheless, we are unaware of an amide hydrolysis mediated in this way by a nearby alcohol. The similarity of the amide methanolysis of **25** to cleavage of other N-acylated oxazolidinones such as the removal of the Evans chiral auxiliary[27] is obvious; however, the facility of this methanolysis is undoubtedly enhanced by the relief of strain.

Conclusion

A four-carbon tether between a pair of 2-pyridones leads to a single trans adduct from intramolecular photocycloaddition. When the tether has a hydroxyl group, hydrogen bonding to a pyridone nitrogen results in solvent-dependent diastereoselectivity for the cycloaddition. The resulting secondary alcohol of the major photoproduct can act to relay a Boc carbonyl group onto the neighboring amide nitrogen, leading to a very facile hydrolytic cleavage of the amide bond. This hydrolysis chemistry provides a gentle method for manipulation of the pyridone photoproducts that will prove to be useful in the synthetic application of this versatile higher-order cycloaddition.

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Experimental Section

4-(1,2-Dihydro-1-methyl-2-oxo-3-pyridinyl)-butanoic Acid from 9. In a modification of the procedure described by Weber,[7] to a solution of $K_3Fe(CN)_6$ (41.6 g, 126 mmol) in 2 N NaOH (180 mL) at 0 °C was added 1-methyl-5,6,7,8-tetrahydroquinolinium iodide **9**[7] (3.47 g, 12.62 mmol) in 2 N NaOH (126 mL) over 10 min. After 30 min of stirring, the mixture was allowed to warm to room temperature for 45 min and then heated with a 50 °C oil bath for another 3 h. The solution was cooled, saturated with NaCl, and then extracted with $CHCl_3$. The aqueous phase was acidified to pH 4 with concentrated H_2SO_4, saturated with NaCl, and then extracted with $CHCl_3$. The combined organic extracts were dried over $MgSO_4$ and concentrated to give a red-black solid. Flash chromatography (60:40:1 toluene/acetone/formic acid) afforded the titled product as a colorless solid (968 mg, 40%): $R_f = 0.28$ (60:40:1 toluene/acetone/formic acid); ^{1}H NMR ($CDCl_3$) δ 7.27−7.22 (m, 2H), 6.19 (t, 1H, $J = 6.7$ Hz), 3.58 (s, 3H), 2.64 (t, 2H, $J = 7.2$ Hz), 2.38 (t, 2H, $J = 7.2$ Hz), 1.94 (quintet, 2H, $J = 7.2$ Hz).

Methyl 4-(1,2-Dihydro-1-methyl-2-oxo-3-pyridinyl)-butanoate. To a solution of 4-(1,2-dihydro-1-methyl-2-oxo-3-pyridinyl)-butanoic acid (967.8 mg, 4.96 mmol) in methanol (20 mL) at room temperature was added concentrated H_2SO_4 (0.4 mL). After stirring for 18 h, the solution was neutralized with methanolic sodium hydroxide, dried over Na_2SO_4, and filtered through Celite. Concentration gave a yellow oil. Flash chromatography (60:40:1 toluene/acetone/formic acid) afforded the titled product as a colorless oil (988 mg, 95%): $R_f = 0.44$ (60:40:1 toluene/acetone/formic acid); ^{1}H NMR ($CDCl_3$) δ 7.17 (m, 2H), 6.08 (t, 1H, $J = 6.9$ Hz), 3.65 (s, 3H), 3.53 (s, 3H), 2.56 (t, 2H, $J = 7.8$ Hz), 2.36 (t, 2H, $J = 7.8$ Hz), 1.93 (quintet, 2H, $J = 7.8$ Hz).

3-(4-Hydroxybutyl)-1-methyl-2(1*H*)-pyridinone 10. To a solution of methyl 4-(1,2-dihydro-1-methyl-2-oxo-3-pyridinyl)-butanoate (222 mg, 1.06 mmol) in THF (2 mL) at 0 °C was added DIBAL (3.18 mL of a 1 M solution in hexame, 3.18 mmol). After the mixture was stirred for 2 h, methanol (1 mL) was added and the mixture warmed to room temperature. A saturated solution of Rochelle salt (2 mL) was added to the mixture, and the aqueous phase was extracted with methylene chloride. The combined organic phases were dried over Na_2-

SO_4 and concentrated to give a yellow oil. Flash chromatography (100:8 CH_2Cl_2/methanol) gave **10** as a colorless oil (159 mg, 83%): R_f = 0.36 (100:8 CH_2Cl_2/methanol); ^{1}H NMR ($CDCl_3$) δ 7.11 (d, 2H, J = 6.0 Hz), 6.04 (t, 1H, J = 6.6 Hz), 3.59 (t, 2H, J = 5.5 Hz), 3.46 (s, 3H), 3.35 (s, 1H), 2.47 (t, 2H, J = 7.1 Hz), 1.60−1.52 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 163.0, 136.1, 135.6, 133.3, 105.6, 61.9, 37.6, 32.0, 30.0, 24.3; IR (neat) 3394, 3087, 3011, 2934, 2861, 1646, 1583, 1560, 1407, 1062, 766 cm^{-1}; exact mass calcd for $C_{10}H_{15}NO_2$ 181.1103, found 181.1099.

4-(1,2-Dihydro-1-methyl-2-oxo-3-pyridinyl)-butanal 6. To a solution of oxalyl chloride (0.348 mL, 3.92 mmol) in methylene chloride (10 mL) at −78 °C was added DMSO (0.539 mL, 7.83 mmol). After gas evolution ceased, alcohol **10** (322.3 mL, 1.78 mmol) in methylene chloride (5 mL) was added dropwise. The mixture was allowed to warm to −35 °C over 30 min, and then triethylamine (1.355 mL, 9.85 mmol) was added. After the mixture was warmed to room temperature, concentrated HCl (1 mL) was added. The organic phase was washed with saturated $NaHCO_3$ (10 mL), and the aqueous phases were extracted with methylene chloride. The combined organics were dried over Na_2SO_4 and concentrated to give a yellow oil. Flash chromatography (60:40 CH_2Cl_2/acetone) afforded **6** as a colorless oil (264.2 mg, 87%): R_f = 0.54 (60:40 CH_2Cl_2/acetone); ^{1}H NMR ($CDCl_3$) δ 9.69 (m, 1H), 7.14−7.09 (m, 2H), 6.02 (t, 1H, J = 6.9 Hz), 3.46 (s, 3H), 2.51−2.37 (m, 4H), 1.86 (quintet, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 202.3, 162.7, 136.4, 136.0, 132.0, 105.3, 43.2, 37.5, 30.3, 20.7; IR (neat) 3016, 2937, 2867, 2735, 1714, 1644, 1562, 1110, 769 cm^{-1}; exact mass calcd for $C_{10}H_{13}NO_2$ 179.0947, found 179.0946.

2-Fluoro-3-iodopyridine.[12] To a solution of diisopropylamine (7 mL, 50 mmol) in THF (200 mL) at −20 °C was added *n*-BuLi (20 mL of a 2.5 M solution in hexane, 50 mmol). After stirring for 30 min, the mixture was cooled to −78 °C and a solution of 2-fluoropyridine (4.39 mL, 0.050 mmol) in THF (50 mL) was added over 10 min. The resulting yellow suspension was stirred for 4 h at −78 °C at which time a solution of iodine (12.7 g, 50 mmol) in THF (45 mL) was added. After stirring for 1 h at −78 °C, a mixture of H_2O (10 mL) and THF (50 mL) was added. After the mixture was warmed to 0 °C, additional water (50 mL) was added, followed by solid sodium thiosulfate. The aqueous phase was extracted with ether; the combined organics were dried over Na_2SO_4 and concentrated to give a brown oil that was purified by Kugelrohr distillation to give the 2-fluoro-3-iodopyridine as a colorless solid (10.1 g, 91%). Recrystallization from hexane/ether (50:1) gave an analytical sample: R_f = 0.61 (1:6 ethyl acetate/hexane); mp = 42−43 °C (lit.[12] 43 °C); ^{1}H NMR ($CDCl_3$) δ 8.15 (m, 2H), 6.95 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 145.7, 142.9, 142.7, 118.3, 118.2; IR (KBr) 3438, 2958, 2920, 1578, 1559, 1427, 1406, 1251, 1237 cm^{-1}.

When an excess of LDA was used, 2-fluoro-3,4-diiodopyridine[28] could be isolated as from the residue of the Kugelrohr distillation: R_f = 0.63 (1:6 ethyl acetate/hexane); mp = 107−109 °C (lit.[28] 114 °C); ^{1}H NMR ($CDCl_3$) δ 7.86 (d, 1H, J = 5.0 Hz), 7.66 (dd, 1H, J = 0.6, 5.0 Hz); ^{13}C NMR ($CDCl_3$) δ 142.6, 142.4, 127.74, 127.68, 95.5; IR (KBr) 1569, 1551, 1516, 1426, 1365 cm^{-1}. Anal. Calcd for $C_5H_2FI_2N$: C, 17.21; H 0.85; N, 4.01. Found: C, 17.39; H, 0.65; N, 3.97.

4-(2-Fluoro-3-pyridinyl)-3-butyn-1-ol (11). To a suspension of 2-fluoro-3-iodopyridine (25.5 g, 114 mmol), $(PPh_3)_2PdCl_2$ (3.37 g, 4 mol %), and CuI (430 mg, 2 mol %) in triethylamine (450 mL) at 0 °C was added 3-butyn-1-ol (9.52 mL, 126 mmol). After stirring for 9 h, water (500 mL) was added and the aqueous phase was extracted with ether. The combined organics were washed twice with 10% HCl, dried over Na_2SO_4, and concentrated to give a black oil. Kugelrohr distillation gave **11** as a colorless oil (17.9 g, 95%): R_f = 0.29 (4:6 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$) δ 8.10 (d, 1H, J = 4.7 Hz), 7.78 (m, 1H), 7.12 (m, 1H), 3.84 (q, 2H, J = 6.3 Hz), 2.72 (t, 2H, J = 6.3 Hz), 2.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 164.3, 146.1, 143.6, 121.0, 107.8, 94.1, 74.0, 60.8, 23.9; IR (neat) 3377, 3072, 2946, 2866, 2237, 1602, 1438, 1255, 1048 cm^{-1}; exact mass calcd for C_9H_8FNO 165.0590, found 165.0591.

2-Fluoro-3-(4-hydroxybutyl)-pyridine. To a solution of **11** (17.94 g, 109 mmol) in a mixture of ethanol (25 mL) and ethyl acetate (25 mL) was added 10% Pd/C (4.9 g), and the mixture was stirred under 1 atm of hydrogen for 34 h. Filtration and concentration of the filtrate gave a quantitative yield of the title compound as a yellow oil: R_f = 0.28 (1:1 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$) δ 8.00 (d, 1H, J = 4.7 Hz), 7.61−7.54 (m, 1H), 7.10−7.05 (m, 1H), 3.64 (t, 2H, J = 6.0 Hz), 2.63 (t, 2H, J = 7.4 Hz), 2.16 (s, 1H), 1.71−1.56 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 163.4, 144.8, 140.8, 123.9, 121.4, 62.2, 32.0, 28.5, 25.7; IR (neat) 3394, 3011, 2934, 2861, 1646, 1583, 1560, 1407, 1223, 1062, 766 cm^{-1}; exact mass calcd for $C_9H_{12}FNO$ 169.0903, found 169.0901.

4-(2-Fluoro-3-pyridinyl)-butyl Acetate. To a solution of 2-fluoro-3-(4-hydroxybutyl)-pyridine (220 mg, 1.30 mmol) and DMAP (6.11 mg, 0.050 mmol) in methylene chloride (5 mL) at room temperature were added acetic anhydride (0.245 mL, 2.60 mmol) and triethylamine (0.40 mL, 2.6 mmol). After the mixture was stirred for 12 h, water (5 mL) was added and the aqueous phase was extracted with methylene chloride. The combined organics were dried over Na_2SO_4, filtered, and concentrated to give a yellow oil. Flash chromatography (4:6 ethyl acetate/hexane) gave the title compound as a colorless oil (249 mg, 91%): R_f = 0.58 (1:1 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$) δ 8.04 (d, 1H, J = 4.4 Hz), 7.61−7.55 (m, 1H), 7.11−7.08 (m, 1H), 4.08 (t, 2H, J = 5.6 Hz), 2.67−2.63 (t, 2H, J = 6.8 Hz), 2.03 (s, 3H), 1.68−1.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 171.1, 161.6, 145.1, 144.7, 123.6, 121.4, 63.9, 28.4, 28.1, 25.9, 20.9; IR (neat) 3063, 2952, 2868, 1736, 1604, 1578, 1434, 1366, 1243, 1046, 801 cm^{-1}; exact mass calcd for $C_{11}H_{14}FNO_2$ 211.1009, found 211.1006.

4-(1,2-Dihydro-1-methyl-2-oxo-3-pyridinyl)-butyl Acetate (12). To a solution of 4-(2-fluoro-3-pyridinyl)-butyl acetate (1.453 g, 6.88 mmol) in chloroform (10 mL) at 0 °C was added dimethyl sulfate (3.9 mL, 41.3 mmol) over 4 min. The reaction mixture was heated to reflux for 15 h and cooled to room temperature, and a mixture of triethylamine/acetic acid/ethanol (3:2:2, 47.5 mL) was added. After the mixture was refluxed for an additional 1 h, water (5 mL) was added. The aqueous phase was extracted with methylene chloride; the combined organics were dried over Na_2SO_4 and concentrated to give a yellow oil. Flash chromatography (100:5 methylene chloride/methanol) gave **12** as a colorless oil (1.276 g, 83%): R_f = 0.60 (100:8 methylene chloride/methanol); ^{1}H NMR ($CDCl_3$) δ 7.09 (m, 2H), 6.00 (t, 1H, J = 6.6 Hz), 3.99 (t, 2H, J = 5.7 Hz), 3.45 (s, 3H), 2.46 (t, 2H, J = 6.6 Hz), 1.94 (s, 3H), 1.59−1.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 170.9, 162.7, 135.9, 135.7, 132.8, 105.2, 64.2, 37.5, 30.2, 28.2, 24.4, 20.8; IR (neat) 3120, 3077, 2951, 2867, 1732, 1649, 1589, 1560, 1247, 1037, 764 cm^{-1}; exact mass calcd for $C_{12}H_{17}NO_3$ 223.1209, found 223.1209.

3-(4-Hydroxybutyl)-1-methyl-2(1*H*)-pyridinone (10) from 12. To a solution of **12** (638.0 mg, 2.86 mmol) in a mixture of methanol (20 mL) and water (2 mL) was added K_2CO_3 (591 mg, 4.29 mmol). After 1 h of stirring, the mixture was filtered, concentrated, and extracted with methylene chloride. The organic phase was dried over Na_2SO_4 and concentrated to give a pale yellow oil. Flash chromatography (10:1 methylene chloride/methanol) gave **10** as a colorless oil (492.9 mg, 95%).

3-[4-(6-Benzyloxy-2-pyridinyl)-4-hydroxybutyl]-1-methyl-2(1*H*)-pyridinone (14). To a solution of 6-bromo-2-benzyloxypyridine (4.27 g, 16.2 mmol) in THF (50 mL) at −78 °C was added *n*-butyllithium (6.03 mL of a 2.5 M solution in hexane, 15.1 mmol) over 5 min. The solution was stirred for 40 min, and then aldehyde **6** (1.93 g, 10.8 mmol) in THF (30 mL) was added slowly over 20 min. The mixture was stirred for 1 h and quenched with saturated NH_4Cl (4 mL) and the aqueous phase extracted with methylene chloride. The combined organics were dried over Na_2SO_4 and concentrated to give a brown oil. Flash chromatography (60:40:8 ethyl acetate/hexane/methanol) afforded **14** as pale yellow oil (1.43 g, 38%): R_f = 0.57 (60:40:8 ethyl acetate/hexane/methanol); ^{1}H NMR ($CDCl_3$) δ 7.56 (t, 1H, J = 7.8 Hz), 7.45−7.26 (m, 5H), 7.16 (d, 2H, J = 6.6 Hz), 6.83 (d, 1H, J = 7.1 Hz), 6.67 (d, 1H, J = 8.0 Hz), 6.08 (t, 1H, J = 6.9 Hz), 5.38 (s, 2H), 4.68 (m, 1H), 3.90 (d, 1H, J = 6.0 Hz), 3.53 (s, 3H), 2.61−2.54 (m, 2H), 1.88−

1.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 163.0, 162.6, 160.1, 139.2, 137.2, 135.9, 135.6, 133.3, 128.3, 127.8, 127.7, 112.9, 109.2, 105.4, 72.5, 67.5, 37.8, 37.6, 30.2, 24.0; IR (neat) 3384, 3064, 3031, 2940, 2865, 1647, 1576, 1448, 1022, 753 cm^{-1}; exact mass calcd for $C_{22}H_{24}N_2O_3$ 364.1781, found 364.1789.

3-[4-(1,6-Dihydro-6-oxo-2-pyridinyl)-4-hydroxybutyl]-1-methyl-2(1*H*)-pyridinone (2) and 3-[4-(1,6-Dihydro-6-oxo-2-pyridinyl)-butyl]-1-methyl-2(1*H*)-pyridinone (15). To a solution of **14** (1.32 g, 3.76 mol) in ethanol (20 mL) was added 10% Pd/C (412.3 mg). After 20 h of stirring at room temperature under 1 atm of hydrogen, the mixture was filtered. Concentration gave a pale yellow oil. Flash chromatography (10:1 CH_2Cl_2/methanol) gave **2** as a colorless oil (589.6 mg, 45%) and **15** (214.3 mg, 17%) as a colorless solid.

Compound 2:[6] R_f = 0.25 (100:8 CH_2Cl_2/methanol); ^{1}H NMR (CD_3OD) δ 7.56−7.48 (m, 2H), 7.37 (d, 1H, J = 6.6 Hz), 6.40−6.27 (m, 3H), 4.58 (t, 1H, J = 5.4 Hz), 3.56 (s, 3H), 2.55 (t, 2H, J = 6.6 Hz) 1.75−1.64 (m, 4H).

Compound 15: R_f = 0.38 (100:8 CH_2Cl_2/methanol); mp = 111.7−112.9 °C; ^{1}H NMR (CD_3OD) δ 7.73 (dd, 1H, J = 9.0, 6.9 Hz), 7.16 (d, 2H, J = 6.9 Hz), 6.37 (d, 1H, J = 9.3 Hz), 6.08−6.00 (m, 2H), 3.54 (s, 3H), 2.65−2.53 (m, 4H), 1.72−1.61 (m, 4H); ^{13}C NMR (CD_3OD) δ 165.6, 163.1, 150.0, 141.5, 136.2, 135.7, 133.1, 116.8, 105.6, 104.9, 37.8, 32.6, 29.9, 28.2, 27.6; IR (neat) 3418, 3287, 3124, 2935, 2861, 1646, 1617, 1581, 1561, 1455 cm^{-1}; exact mass calcd for $C_{15}H_{18}N_2O_2$ 258.1364, found 258.1371.

(3α,4*β*,6α*β*,10αα)-4,5,7,8,9,10-Hexahydro-5-methyl-3,-10a:4,6a-dietheno-1,5-benzodiazocine-2,6(1*H*,3*H*)-dione (16). Dry nitrogen was bubbled for 15 min through a methanol (2.4 mL) solution of bis-2-pyridone **15** (30.0 mg, 0.12 mmol, 50 mM) in a quartz tube. The solution was cooled to 10 °C and irradiated for 22 h with a Pyrex-filtered medium-pressure mercury lamp. Concentration and flash chromatography (7:3:1 ethyl acetate/hexane/methanol) gave **16** (10.0 mg, 33%) as a colorless solid: R_f = 0.26 (7:3:1 ethyl acetate/hexane/methanol); mp = 158.5−159.5 °C; ^{1}H NMR ($CDCl_3$) δ 6.64 (dd, 1H, J = 8.4, 6.9 Hz), 6.30 (dd, 1H, J = 8.4, 1.2 Hz), 6.23 (dd, 1H, J = 8.4, 6.9 Hz), 6.03 (dd, 1H, J = 8.4, 1.5 Hz), 4.15 (ddd, 1H, J = 9.9, 6.9, 1.5 Hz), 3.47 (ddd, 1H, J = 9.9, 6.9, 1.5 Hz), 2.77 (s, 3H), 2.29 (m, 1H), 1.97−1.69 (m, 7H); ^{13}C NMR (CD_3OD) δ 180.6, 179.2, 142.9, 138.4, 134.3, 128.9, 61.2, 59.9, 57.3, 52.5, 36.2, 31.4, 26.9, 15.6, 14.9; IR (neat) 3058, 2926, 2877, 1640, 1646, 1398, 798 cm^{-1}; exact mass calcd for $C_{15}H_{18}N_2O_2$ 258.1328, found 258.1372.

(3α,4*β*,6α*β*,10αα)-4,5,7,8,9,10,11,12,13,14-Decahydro-5-methyl-3,10a:4,6a-diethano-1,5-benzodiazocine-2,6(1*H*,3*H*)-dione (17). To a solution of **16** (24.0 mg, 0.093 mmol) in methanol (4 mL) was added 10% Pd/C (40 mg). After stirring for 20 h under 1 atm of hydrogen, the mixture was filtered through Celite. Concentration gave a pale yellow oil. Flash chromatography (7:3:1 ethyl acetate/hexane/methanol) gave **17** (29.6 mg, 88%) as a colorless solid: R_f = 0.26 (7:3:1 ethyl acetate/hexane/methanol); mp = 219.6−221.0 °C; ^{1}H NMR (CD_3OD) δ 4.00 (ddd, 1H, J = 11.1, 6.6, 1.5 Hz), 3.05 (s, 3H), 2.91 (m, 1H), 2.11−1.52 (m, 16H); ^{13}C NMR (CD_3OD) δ 179.5, 178.8, 59.6, 58.1, 50.9, 46.4, 27.4, 36.5, 33.6, 31.1, 30.8, 25.1, 22.2, 16.4, 15.3; IR (KBr) 3423, 2958, 2877, 1670, 1646, 1467, 1406 cm^{-1}; exact mass calcd for $C_{15}H_{22}N_2O_2$ 262.1676, found 262.1683.

(3α,4*β*,6α*β*,10α,10αα)-4,5,7,8,9,10-Hexahydro-10-hydroxy-5-methyl-3,10a:4,6a-dietheno-1,5-benzodiazocine-2,6-(1*H*,3*H*)-dione (1a) and (3α,4*β*,6α*β*,10*β*,10αα)-4,5,7,8,9,10-Hexahydro-10-hydroxy-5-methyl-3,10a:4,6a-dietheno-1,5-benzodiazocine-2,6(1*H*,3*H*)-dione (1b). Dry nitrogen was bubbled for 15 min through a solution of methanol (22.7 mL) containing bis-2-pyridone **2** (311 mg, 1.14 mmol, 50 mM) in a quartz tube. The solution was irradiated for 37 h at 10 °C using a Pyrex-filtered medium-pressure mercury lamp. Concentration of the solution and Flash chromatography (10:1 CH_2Cl_2/methanol) gave trans,syn **1a** (107.7 mg, 35%) and trans,anti **1b** (86.1 mg 28%), both as colorless solids.

Syn Isomer Compound 1a: mp = 213 °C;[6] R_f = 0.30 (10:1 CH_2Cl_2/methanol); ^{1}H NMR (CD_3OD) δ 6.66 (dd, 1H, J = 8.8, 7.2 Hz), 6.39 (dd, 1H, J = 8.4, 1.5 Hz), 6.26 (dd, 1H, J = 8.4, 7.2 Hz), 6.00 (dd, 1H, J = 8.4, 1.5 Hz), 4.17 (ddd, 1H, J = 9.6, 7.2, 1.2 Hz), 4.03−3.99 (m, 1H), 3.50 (ddd, 1H, J = 9.6, 7.2, 1.2 Hz), 2.77 (s, 3H), 2.36−2.26 (m, 1H), 2.06−1.70 (m, 5H).

Anti Isomer Compound 1b: mp = 204−207 °C;[6] R_f = 0.36 (10:1 CH_2Cl_2/methanol); ^{1}H NMR (CD_3OD) δ 6.70 (dd, 1H, J = 8.7, 1.2 Hz), 6.61 (dd, 1H, J = 8.7, 6.6 Hz), 6.28 (dd, 1H, J = 8.7, 6.6 Hz), 5.80 (dd, 1H, J = 8.7, 1.2 Hz), 4.14 (ddd, 1H, J = 9.6, 6.6, 1.2 Hz), 3.97−3.92 (m, 1H), 3.48 (ddd, 1H, J = 9.6, 6.6, 1.5 Hz), 2.76 (s, 3H), 2.46−2.31 (m, 1H), 2.01−1.67 (m, 5H).

(3α,4*β*,6α*β*,10α,10αα)-4,5,7,8,9,10,11,12,13,14-Decahydro-10-hydroxy-5-methyl-3,10a:4,6a-diethano-1,5-benzodiazocine-2,6(1*H*,3*H*)-dione (18). To a solution of **1a** (32.8 mg, 0.12 mmol) in methanol (4 mL) was added 10% Pd/C (27.1 mg). After stirring for 20 h at room temperature under 1 atm of hydrogen, the mixture was filtered through Celite. Concentration gave a pale yellow oil. Flash chromatography (10:1 CH_2Cl_2/methanol) gave **18**[6] (29.6 mg, 89%) as a colorless solid: R_f = 0.48 (10:1 CH_2Cl_2/methanol); mp = 232.5−233.1 °C; ^{1}H NMR (CD_3OD) δ 4.02 (m, 1H), 3.68 (t, 1H, J = 6.6 Hz), 3.05 (s, 3H), 2.94 (m, 1H), 2.49−2.40 (m, 1H), 2.16−1.37 (m, 13H); ^{13}C NMR (CD_3OD) δ 179.8, 178.3, 73.1, 62.2, 58.0, 51.8, 46.3, 37.5, 31.5, 29.8, 29.5, 25.0, 24.0, 22.2, 16.2; IR (neat) 3388, 2948, 2880, 1727, 1650, 1643, 1469, 1329, 731 cm^{-1}.

(3α,4*β*,6α*β*,10*β*,10αα)-4,5,7,8,9,10,11,12,13,14-Decahydro-10-hydroxy-5-methyl-3,10a:4,6a-diethano-1,5-benzodiazocine-2,6(1*H*,3*H*)-dione (19). To a solution of **1b** (29.2 mg, 0.11 mmol) in methanol (3 mL) was added 10% Pd/C (19.5 mg). After stirring for 20 h at room temperature under 1 atm of hydrogen, the mixture was filtered through Celite. Concentration gave a pale yellow oil. Flash chromatography (10:1 CH_2Cl_2/methanol) gave **19**[6] (26.9 mg, 91%) as colorless solid: R_f = 0.39 (10:1 CH_2Cl_2/methanol); mp = 257.2−258.5 °C; ^{1}H NMR (CD_3OD) δ 4.00 (ddd, 1H, J = 11.1, 6.4, 1.2 Hz), 3.86 (dd, 1H, J = 11.4, 5.7 Hz), 3.06 (s, 3H), 2.91 (ddd, 1H, J = 11.1, 5.1, 1.8 Hz), 2.32−1.37 (m, 14H); ^{13}C NMR (CD_3OD) δ 179.7, 178.5, 70.4, 63.7, 58.3, 52.4, 46.2, 37.4, 32.0, 25.3, 25.0, 24.5, 21.8, 17.5; IR (neat) 3417, 2955, 2852, 1642, 1469, 1450, 1210, 799 cm^{-1}; exact mass calcd for $C_{15}H_{22}N_2O_3$ 278.1625, found 278.1642.

(3α,4*β*,6α*β*,10α,10αα)-4,5,7,8,9,10,11,12,13,14-Decahydro-10-[[(1,1-dimethylethoxy)carbonyl]oxy]-5-methyl-3,10a:4,6a-diethano-1,5-benzodiazocine-2,6(1*H*,3*H*)-dione (20). To a solution of **18** (102.3 mg, 0.37 mmol) in methylene chloride (10 mL) were added di-*tert*-butyl dicarbonate (200.8 mg, 0.93 mmol), DMAP (7 mg), and triethylamine (0.14 mL, 0.93 mmol) at room temperature. After the mixture was stirred for 15 h, water (2 mL) was added and the aqueous phase was extracted with methylene chloride. The combined organic phases were dried over Na_2SO_4 and concentrated to give a yellow oil. Flash chromatography (70:30:8.3 ethyl acetate/hexane/methanol) gave **20** as a colorless solid (100.9 mg, 72%): R_f = 0.35 (70:30:8.3 ethyl acetate/hexane/methanol); ^{1}H NMR (CD_3OD) δ 4.68−4.64 (m, 1H), 4.05−3.99 (m, 1H), 3.06 (s, 3H), 2.97−2.93 (m, 1H), 2.54−2.44 (m, 1H), 2.24−1.32 (m, 22H); ^{13}C NMR (CD_3OD) δ 179.5, 177.6, 154.2, 83.6, 78.5, 61.6, 58.0, 52.2, 46.3, 37.5, 31.2, 29.9, 29.6, 27.9, 24.9, 21.8, 20.7, 15.8; IR (KBr) 2958, 2883, 1738, 1675, 1649, 1281, 1255, 1160 cm^{-1}; exact mass calcd for $C_{20}H_{31}N_2O_5$ 379.2249, found 379.2233.

Oxazolidinone 21. To a solution of **20** (91.7 mg, 0.24 mmol) in methanol (25 mL) was added K_2CO_3 (400.3 mg, 2.88 mmol). After stirring for 2 h, the mixture was filtered and concentrated. Saturated NH_4Cl (3 mL) was added, and the aqueous phase was extracted with methylene chloride. The combined organic phases were dried over Na_2SO_4 and concentrated to give a colorless oil. Flash chromatography (70:30:9 ethyl acetate/hexane/methanol) gave **21** (30.6 mg, 50%) as a colorless solid and **20** (7.0 mg, 10%); R_f = 0.43 (70:30:9 ethyl acetate/hexane/methanol); mp = 236.5−237.5 °C; ^{1}H NMR (CD_3OD) δ 4.28−4.25 (m, 1H), 4.09−4.06 (m, 1H), 3.69 (s, 3H), 2.96 (s, 3H), 2.89 (m, 1H), 2.17−1.54 (m, 14H); ^{13}C NMR (CD_3OD) δ 177.3, 174.8, 161.3, 86.5, 66.2, 59.3, 52.5, 47.7, 46.5, 37.6, 35.1, 24.2, 32.3, 26.0, 21.7. 19.2, 18.8; IR (neat) 2939, 2877, 1745, 1641, 1379, 1299, 1250, 1054, 992, 733 cm^{-1}; exact mass calcd for $C_{17}H_{24}N_2O_5$ 336.1679, found 336.1682.

(3α,4*β*,6α*β*,10*β*,10αα)-4,5,7,8,9,10,11,12,13,14-Decahydro-10-[[(1,1-dimethylethoxy)carbonyl]oxy]-5-methyl-3,10a:4,6a-diethano-1,5-benzodiazocine-2,6(1*H*,3*H*)-dione (22). To a solution of **19** (17.9 mg, 0.064 mmol) in methylene chloride (5 mL) at room temperature were added di-*tert*-butyl dicarbonate (35.2 mg, 0.16 mmol), DMAP (5 mg), and triethylamine (0.10 mL, 0.67 mmol). After the mixture was stirred for 7 h, water (1 mL) was added and the aqueous phase was extracted with methylene chloride. The combined organic phases were dried over Na_2SO_4 and concentrated to give a yellow oil. Flash chromatography (20:1 methylene chloride/methanol) gave **22** as a colorless solid (24.0 mg, 99%): $R_f = 0.61$ (10:1 methylene chloride/methanol); ^{1}H NMR ($CDCl_3$) δ 6.32 (s, 1H), 4.95−4.89 (m, 1H), 3.87−3.81 (m, 1H), 3.07 (s, 3H), 2.96−2.92 (m, 1H), 2.44−1.48 (m, 23H); ^{13}C NMR (CD_3OD) δ 179.4, 177.9, 154.7, 83.4, 76.8, 62.5, 58.2, 52.7, 46.1, 37.4, 31.8, 31.4, 28.0, 26.0, 25.1, 21.8, 21.5, 16.9; IR (neat) 2954, 2883, 1739, 1675, 1650, 1282, 1257, 1162, 1090, 733 cm^{-1}; exact mass calcd for $C_{20}H_{30}N_2O_5$ 378.2417, found 378.2153.

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Supporting Information Available: Proton NMR and COSY spectra for new compounds and crystallographic data for **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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