A 2-Pyridone Photo-[4 + 4] Approach to the Taxanes

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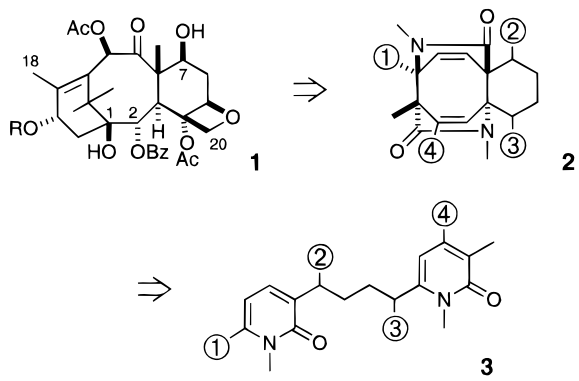
Abstract: Pyridones tethered by a four-carbon chain at the 3- and 6'-positions can undergo [4 + 4] photocycloaddition to simultaneously form three, but not four, tetrasubstituted carbons. In a study directed at the taxanes, photocycloaddition of **28** was found to be fully controlled by a (*tert*-butyldimethylsilyl)oxy group on the tether, to give a photoproduct with five stereogenic centers and both quaternary carbons found in taxol (paclitaxel). This photoproduct proved to be unstable to silica gel, but saturation of one alkene gave a stable product (**30**). Epoxidation of the enol ether of **30** proceeds exclusively from one face of the cyclooctene ring, demonstrating the facial bias of the polycyclic system and correctly introducing the C-2 stereogenic center of taxol. As part of this study, 4-methoxy-2-pyridones, known to be inert to [4 + 4] photodimerization, were found to undergo [4 + 4] photocycloaddition with 4-unsubstituted-2-pyridones both inter- and intramolecularly.

For more than a decade, the acme of eight-membered ring natural product synthesis[1] has been taxol (**1**),[2] a diterpene alkaloid with proven efficacy against several important human cancers[3] and potentially broader clinical applications.[4] More than 100 naturally occurring taxanes have been described,[5] and two of these have been prepared by total synthesis.[6−8]

Formation of the central eight-membered ring of taxol, with its two quaternary and five stereogenic centers, has been a major focus of much of the synthetic work,[1,2] as cyclooctane has long been recognized as the most difficult cycloalkane to make.[9] These difficulties have manifest in a number of synthetic studies, including two of the three taxol syntheses, where formation of the eight-membered ring was the lowest yield step. As a method for preparing cyclooctanes, the [4 + 4] photocycloaddition[10] of 2-pyridones, both inter-[11] and intramolecularly,[12−14] is an efficient process that utilizes simple, aromatic substrates. The overlap of the intramolecular 2-pyridone photoproduct **2** with the skeleton of taxol has led us to explore the photochemistry of molecules such as **3**.[15]



Photodimerization of 2-pyridones proceeds exclusively head-to-tail,[16] and this selectivity is reinforced by sites of attachment of the four-carbon tether in **3** and in the three-carbon tether of

[⊗] Abstract published in *Advance ACS Abstracts*, October 15, 1996.

(1) For a review, see: Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757−5821.

(2) Reviews of taxol chemistry include the following: Kingston, D. G. I. *Pharmacol. Ther.* **1991**, *52*, 1−34. Swindell, C. S. *Org. Prep. Proc. Int.* **1991**, *23*, 465−543. Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1−192. Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15−44. Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemp. Org. Synth.* **1994**, *1*, 47−75. *Taxol®: Science and Applications*; Suffness, M., Ed.; CRC: New York, 1995. *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995.

(3) For reviews, see: Rowinsky, E. K.; Onetto, N.; Canetta, R. M.; Arbuck, S. G. *Semin. Oncol.* **1992**, *19*, 646−662. Runowicz, C. D.; Wiernik, P. H.; Einzig, A. I.; Goldberg, G. L.; Horwitz, S. B. *Cancer* **1993**, *71*, 1591−1596. See also ref 2.

(4) Woo, D. D. L.; Miao, S. Y. P.; Pelayo, J. C.; Woolf, A. S. *Nature (London)* **1994**, *368*, 750−753.

(5) See ref 2. See also, *inter alia*, Appendino, G.; Tagliapietra, S.; Özen, H. C.; Garibaldi, P.; Gabetta, B.; Bombardelli, E. *J. Nat. Prod.* **1993**, *56*, 514−520. Liang, J.; Kingston, D. G. I. *J. Nat. Prod.* **1993**, *56*, 594−599. Appendino, G.; Barboni, L.; Garibaldi, P.; Bombardelli, E.; Gabetta, B.; Viterbo, D. *J. Chem. Soc., Chem. Commun.* **1993**, 1587−1589. Li, B.; Tanaka, K.; Fuji, K.; Sun, H.; Taga, T. *Chem. Pharm. Bull.* **1993**, *41*, 1672−1673. Zhang, H.; Takeda, Y.; Minami, Y.; Yoshida, K.; Matsumoto, T.; Xiang, W.; Mu, O.; Sun, H. *Chem. Lett.* **1994**, 957−960. Appendino, G. *Nat. Prod. Rep.* **1995**, *12*, 349−360 and references therein.

(6) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597−1598. Holton, R. A.; Kim, H.-B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599−1600.

(7) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature (London)* **1994**, *367*, 630−634. Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624−633. Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634−644. Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645−652. Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653−659.

(8) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723−1726. Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843−2859.

(9) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102.

(10) For a review, see: Sieburth, S. McN.; Cunard, N. T. *Tetrahedron* **1996**, *52*, 6251−6282.

(11) (a) Nakamura, Y.; Kato, T.; Morita, Y. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1187−1191. (b) Matsushima, R.; Terada, K. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1445−1448.

(12) Sieburth, S. McN.; Chen, J.-l. *J. Am. Chem. Soc.* **1991**, *113*, 8163−8164.

(13) Sieburth, S. McN.; Joshi, P. V. *J. Org. Chem.* **1993**, *58*, 1661−1663.

(14) Sieburth, S. McN.; Hiel, G.; Lin, C.-H.; Kuan, D. P. *J. Org. Chem.* **1994**, *59*, 80−87.

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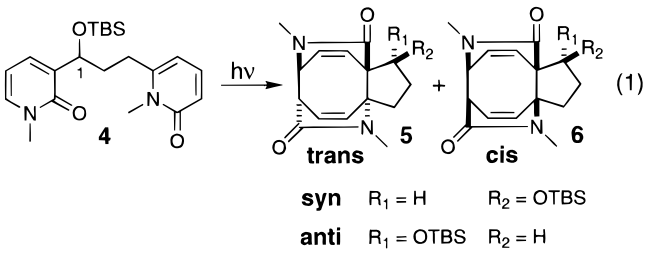
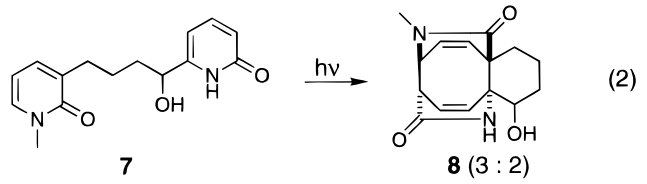
photosubstrates such as **4** (eq 1). In the latter case, yields of cycloadducts **5** and **6** can exceed 90%. With a bulky substituent at C-1, such as the (*tert*-butyldimethylsilyl)oxy group in **4**, the anti isomer is formed with high diastereoselectivity (98−99%).[14] In all cases of a three-carbon tether, however, mixtures of trans and cis isomers are formed in ratios of 2−3:1.[14,17]

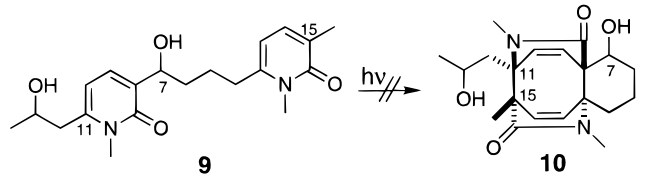


Four-carbon-tethered substrates are less well studied, but an early example established the viability of this method for forming the 8−6 carbocyclic ring system (eq 2).[12] In contrast to **4**, irradiation of **7** gave only the trans isomers of **8**, and stereogenic control by the tether alcohol was rather low.



Results and Discussion

Following the successful cycloaddition of **7**, we turned our attention to bis-2-pyridone **9** as a potential entry into the taxanes. Compound **9** differs from **7** in four ways: a methyl group at C-15 (taxol numbering), a 2-hydroxy-1-propyl group at C-11, location of the tether hydroxyl group at C-7 rather than at C-4, and *N*-methylation of both pyridones. The anticipated photoproduct **10** would contain all but two of the carbons of taxol, C-18 and C-20.



Unfortunately, irradiation of **9** and silylated alcohol derivatives, in a variety of solvents, failed to give any characterizable photoproducts.[18] Extended irradiation times led only to a slow degradation. A possible cause of the resistance of **9** to undergo cycloaddition was the presence of the two additional pyridone substituents, compared to **7**, both of which were at sites involved in carbon−carbon bond formation. Thus, cycloaddition to give **10** would require simultaneous formation of four tetrasubstituted carbons, whereas two tetrasubstituted carbons were created when **8** was formed.[19]

Conformational analysis of the parent system **11** reinforced the idea that the photostability of **9** was due to full substitution at the four incipient sp^3 carbons. A full conformational search around the five rotatable bonds (stars) in **11** was conducted,[20] with the distance between the ends of the reacting 1,3-dienes restricted to less than 5 Å. The lowest energy conformation is depicted in Figure 1. This structure has a half-chair-like tether conformation and would lead to a trans product. The most striking aspect of this conformation is the distance between the reacting ends of the 1,3-dienes. The distance between the internal carbons (triangles) is nearly 0.5 Å larger than the distance between the external carbons (bold crosses). All of the lower energy conformations have similar distances between the reaction centers, an apparent consequence of the four-atom tether. In this conformation, the methyl and propyl groups in **9** would experience serious steric repulsions.[21] Intriguingly, a similar conformational search with the three-carbon-tethered molecule **12** leads to an equally nonparallel, but inverse, arrangement of the two pyridones: the internal carbons are closer than the external carbons by more than 0.5 Å. If the two carbon−carbon bonds formed in the [4 + 4] cycloaddition can be formed asynchronously, and if the distances in these ground state conformations reflect the ordering of bond formation, the molecular model of **12** suggests that formation of four tetrasubstituted carbons *might* be possible in the three-carbon tether case. This conjecture remains untested.

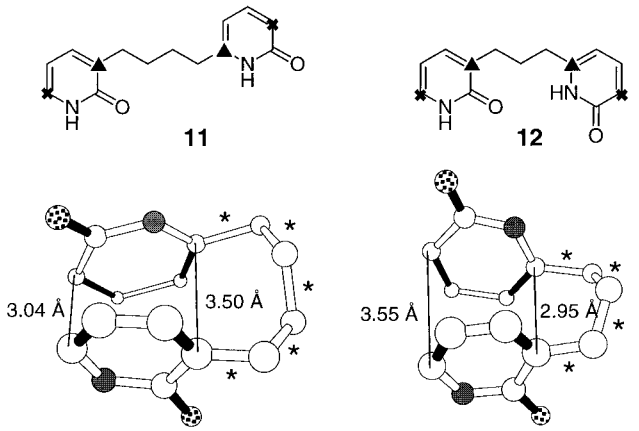


Figure 1. Conformational analysis of **11** and **12** (only nonparallel arrangements of the pyridones).

On the basis of this molecular modeling, it seemed clear that if the simultaneous presence of the C-15 methyl and the C-11

(15) A communication describing some of this chemistry has been published; see: Sieburth, S. McN.; Ravindran, K. *Tetrahedron Lett.* **1994**, *35*, 3861−3864.

(16) Except in water; see ref 11a.

(17) Sieburth, S. McN.; Lin, C.-H. *J. Org. Chem.* **1994**, *59*, 3597−3599.

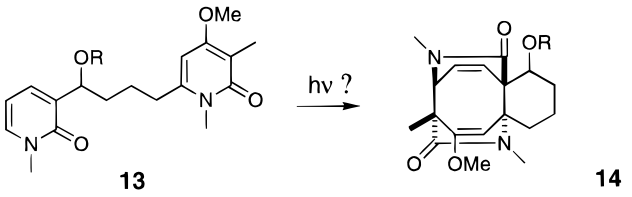
(18) J.-l Chen, research notes, SUNY Stony Brook.

(19) The degree of difficulty for forming three or more tetrasubstituted carbons during a cycloaddition reaction can be calibrated by consulting some of the comprehensive cycloaddition reviews. A review of intramolecular Diels−Alder reactions (Ciganek, E. *Org. React. (N. Y.)* **1984**, *32*, 1−374) contains a single reference to a reaction forming four tetrasubstituted carbons: Paquette, L. A.; Wyvratt, M. J.; Berk, H. C.; Moerck, R. E. *J. Am. Chem. Soc.* **1978**, *100*, 5845−5855. Photo-[2 + 2] reactions are perhaps more generous, with a recent review (Crimmins, M. T.; Reinhold, T. L. *Org. React. (N. Y.)* **1993**, *44*, 297−588) including three systems that produce four tetrasubstituted carbons: Mehta, G.; Srikrishna, A.; Reddy, A. V.; Nair, M. S. *Tetrahedron* **1981**, *37*, 4543−4559. Reid, S. T.; De Silva, D. *Tetrahedron Lett.* **1983**, *24*, 1949−1950. De Keukeleire, D.; Van Audenhove, M.; Van Hijfte, L.; Audenaert, F.; Vandewalle, M. *J. Photochem.* **1985**, *28*, 165−174. Outstanding exceptions, of course, are the thermal [2 + 2] cycloaddition reactions of strained and polyfluorinated alkenes: Dolbier, W. R., Jr.; Lomas, D.; Garza, T.; Harmon, C.; Tarrant, P. *Tetrahedron* **1972**, *28*, 3185−3189. Huisgen, R.; Grashey, R.; Sauer, J. In *The Chemistry of Alkenes*; Patai, S., Ed.; Interscience: New York, 1964; pp 739−953. Roberts, J. D.; Sharts, C. M. *Org. React. (N. Y.)* **1962**, *12*, 1−56.

(20) A Systematic Search of **11** was performed using SYBYL and the Tripos force field.[40] Each rotatable bond was rotated through 360° in 10° increments (6×10^7 conformations). Conformations in which the bonding carbons were more than 5 Å apart were rejected (>99.98%), and for each saved conformation, the steric energy was calculated. Only those conformations within 10 kcal/mol of the lowest energy conformation were kept, giving 8594 conformations.

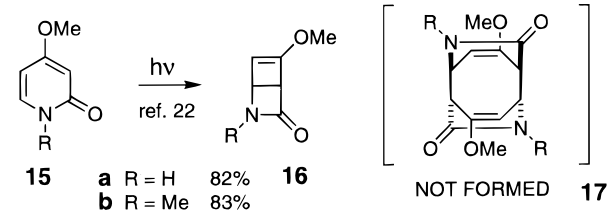
(21) An identical conformational search with two methyl groups at the external (cross) positions of **11** clearly showed this steric interaction, with low-energy conformations highly distorted from that shown for **11** in Figure 1.

hydroxypropyl groups in **9** were responsible for its inability to undergo cycloaddition, then removal of one of these groups should allow the photochemistry to proceed. We therefore elected to prepare **13**, without the hydroxypropyl group, and explore its photochemistry. Should **13** undergo [4 + 4] cycloaddition, three tetrasubstituted carbons would result, including both quaternary carbons required for taxol. The remaining carbons of the A-ring would require later introduction.



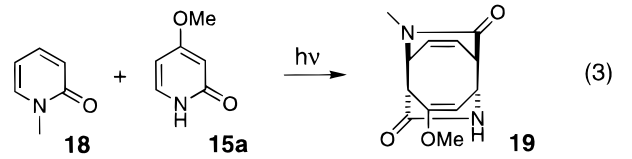
13 **14**

A second and significant difference between **9** and **13** was incorporation of a 4-methoxy-2-pyridone. This group would allow for a straightforward preparation of that portion of **13**, and it would differentiate the alkenes of the product **14**. The potential pitfall, however, was that the 4-methoxy group might present difficulties in the photocycloaddition step. Kaneko has reported that 4-alkoxy-2-pyridones such as **15** *do not* undergo [4 + 4] photodimerization but instead photoisomerize to Dewar pyridones **16**.[22,23]



15 **a** R = H 82% **16** NOT FORMED **17**
b R = Me 83%

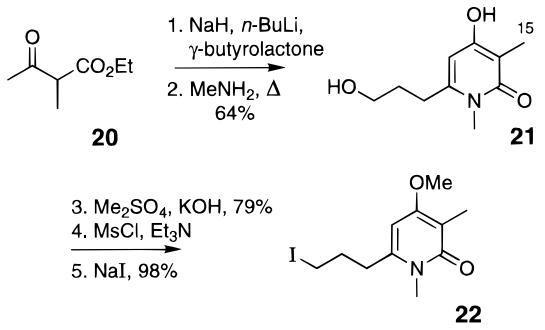
Before preparing **13**, we needed to know whether 4-alkoxy-2-pyridones could undergo [4 + 4] cycloaddition with a 4-unsubstituted-2-pyridone. We therefore briefly investigated the photochemistry of a mixture of *N*-methyl-2-pyridone (**18**) and 4-methoxy-2-pyridone (**15a**). On irradiation of a 1:1 mixture of these substrates in methanol, two major products were isolated as the known trans, head-to-tail [4 + 4] dimer of **18**[11] (20%) and the cross-product **19** (22%), the structure of which was assigned spectroscopically.[24] This experiment confirmed the ability of 4-alkoxy-2-pyridones to participate in [4 + 4] photocycloadditions and set the stage for the preparation of **13**.



18 **15a** **19** (3)

The synthesis of **13** began with the dianion of the commercially available β-keto ester **20** and its condensation with γ-butyrolactone.[25] The yield of this reaction is limited by the inherent acidity of the β,γ-diketo ester product.

Scheme 1. Synthesis of Pyridone **22**



Nevertheless, warming the crude product with aqueous methylamine gave recrystallized pyridone **21** in 64% overall yield from **20**. The C-15 methyl group of **21** exhibits a distinctive ^{13}C NMR chemical shift of 8.9 ppm, characteristic of a methyl group on an aromatic ring flanked by oxygens.[26] Methylation of the more acidic hydroxyl of **21** with dimethyl sulfate proceeded in 79% yield, and the primary alcohol was then converted to an iodide, via the mesylate (98%).

Iodide **22** was coupled with ethoxyethoxy-protected cyanohydrin[27] **23** in a mixture of THF and DMPU to give, after an aqueous workup incorporating both acidic and basic hydrolyses, ketone **24** (69%). The next stage, hydrolysis of the 2-chloropyridine to a 2-pyridone,[28] initially proved problematic;[29] however, two useful procedures were found. The most direct method was *N*-methylation of the chloropyridine by warming with trimethyloxonium tetrafluoroborate followed by refluxing with a mixture of acetic acid, ethanol, and triethylamine (78% overall).[30] Reduction of the resulting ketone gave alcohol **27** (89%). Alternatively, we found that the oxime of ketone **24** was a good source of nucleophilic oxygen.[31] Oxime **25** was readily prepared as an equimolar mixture of *E* and *Z* isomers (75%). Deprotonation of this mixture with sodium hydride and warming to 40 °C gave a clean cyclization of the *Z* isomer. At 60 °C, the *E* isomer also reacted[32] to give, on workup, a 83% yield of isoxazolopyridine **26**. Reductive cleavage of the isoxazole, using Curran's conditions,[33] gave a keto-bis-2-pyridone[34] (58%) that was reduced by sodium borohydride and then *N*-methylated to give **27**. Although this isoxazolopyridine sequence proved reliable, the overall yield from **24** to **27** was

(22) (a) Fujii, H.; Shiba, K.; Kaneko, C. *J. Chem. Soc., Chem. Commun.* **1980**, 537−538. (b) Kaneko, C.; Shiba, K.; Fujii, H.; Momose, Y. *J. Chem. Soc., Chem. Commun.* **1980**, 1177−1178.

(23) This type of photoisomerization was first described for 2-pyridones by Corey and Streith: Corey, E. J.; Streith, J. *J. Am. Chem. Soc.* **1964**, *86*, 950−951. In the absence of a 4-alkoxy group, [4 + 4] dimerization dominates Dewar pyridone formation except in rather dilute (≪0.1 M) solution.[11]

(24) A study of this intermolecular reaction has been reported, see: Sieburth, S. McN.; Lin, C.-H. *Tetrahedron Lett.* **1996**, *37*, 1141−1144.

(25) Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 1343−1351.

(26) The low chemical shift for this methyl group appears to be associated with flanking oxygen and perhaps nitrogen substitution but not carbon or chlorine as can be seen in the chemical shifts of the following *methyl groups (chemical shift, Sadtler spectra reference number): 1,3-diamino-2-*methylbenzene (10.0 ppm, 6007C); 1,3-dihydroxy-2-*methylbenzene (8.5 ppm, 8762C); 1,3-dimethoxy-2-*methylbenzene (8.2 ppm, 4278C); *2,3-dimethyl-1-methoxybenzene (11.5 ppm, 9064C); 1,*2,3-trimethylbenzene (15.1 ppm, 3521C); 1,3-dichloro-2-*methylbenzene (17.2 ppm, 6281C).

(27) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286−5287.

(28) Tieckelmann, H. In *Heterocyclic Compounds*; Abramovitch, R. A., Ed.; John Wiley & Sons: New York, 1974; Vol. 14, Part 3, pp 683−694.

(29) Standard hydrolytic procedures involving acidic or basic hydrolysis (see: Wibaut, J. P.; Haayman, P. W.; van Dijk, J. *Recl. Trav. Chim. Pays-Bas* **1940**, *59*, 202−206) did not lead to useful yields of the desired product.

(30) Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045−1048.

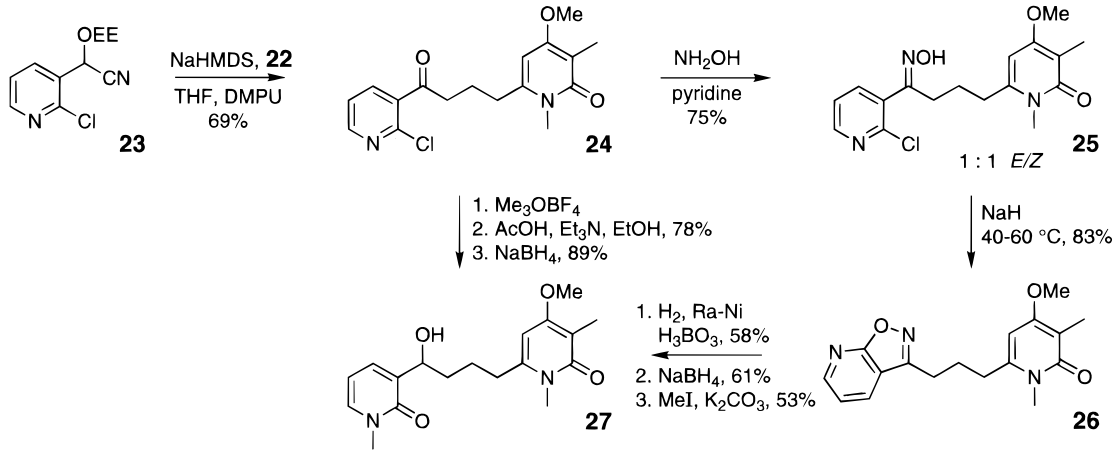
(31) Isoxazolo[5,4-*b*]pyridines have most frequently been prepared by annulation of the pyridine onto a preformed isoxazole; see: Juric, P.; Kocevar, M.; Stanovnik, B.; Tisler, M.; Vercek, B. *Chem. Scripta* **1984**, *23*, 209−211 and references therein.

(32) Oximes and oxime ethers generally have high barriers to *E/Z* isomerization. For discussion and lead references, see: Glaser, R.; Streitwieser, A. *J. Org. Chem.* **1989**, *54*, 5491−5502. Glaser, R.; Streitwieser, A. *J. Am. Chem. Soc.* **1989**, *111*, 7340−7348.

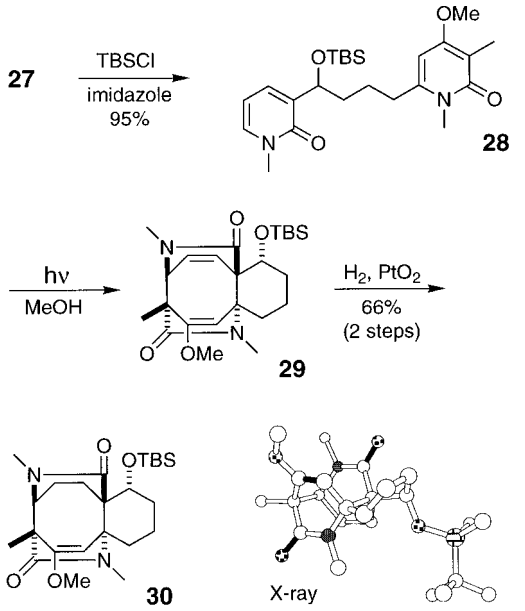
(33) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826−5833.

(34) Previous hydrogenations of the isoxazolo[5,4-*b*]pyridine ring system have been reported to reduce both the N−O bond and the resulting pyridone ring; see: Skötsch, C.; Kohlmeyer, I.; Breitmaier, E. *Synthesis* **1979**, 449−452; U.K. Patent GB 2,117,765, 1983; *Chem. Abstr.* 100:120892x.

Scheme 2. Coupling of **22** and **23**: Two Routes to Bis-2-pyridone **27** from 2-Chloropyridine **(24)**



Scheme 3. Photocycloaddition of **28** To Give **29** as a Single Diastereomer (X-ray Structure of **30**)

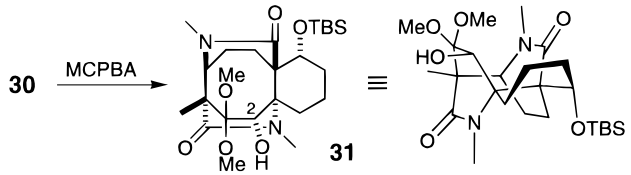


lower than that of the Meerwein's salt procedure. Finally, alcohol **27** was protected as the *tert*-butyldimethylsilyl ether to give **28** (Scheme 3; 95%).

The irradiation of **28** was performed under our standard conditions of a Pyrex-filtered medium-pressure mercury lamp and a 0.05 M solution of the substrate in methanol. The irradiation was periodically interrupted and the solution monitored by TLC. It was with some concern that we noted no change in the TLC, even after 14 h of irradiation. Gratifyingly however, proton NMR revealed a complete absence of starting **28** and the quantitative formation of a *single* photoproduct. On the basis of the propensity of pyridones to yield trans products and the anti selectivity found for the silyloxy group with a three-carbon tether (e.g., **4**), trans-anti stereochemistry was assigned to **29**. Following silica gel chromatography, intended to give an analytical sample, we were surprised to find a quantitative reversion to the starting material **28** had occurred.[35] Repeating the irradiation of **28** returned photoproduct **29** which was then directly hydrogenated to give **30**. This proved to be stable to silica gel, and column chromatography gave pure **30**. Saturation of the alkene in **29** was expected to produce a more stable product, as cycloreversion to aromatic pyridones is no longer possible. Although this reduction removed key functionality, a similarly enhanced stability would be expected from any transformation that removes unsaturation.

The proposed stereochemistry of **30** (and therefore **29**) was confirmed by X-ray crystallography.[15] Notably, the cyclohexane ring was found to be in a boat conformation, with the silyloxy group in a flagpole position. Molecular modeling indicates that this boat conformation, rather than an alternative boat or half-chair, is the energetically preferred conformation for the photoproducts.[15,36]

It can be inferred from the crystal structure of **30** that one face of the enol ether is blocked by an amide group. Epoxidation of the enol ether was therefore expected to proceed stereospecifically. Performing this reaction in methanol[37] led to a spontaneous opening of the labile alkoxy oxirane to form hydroxy ketal **31** (78%) as a single isomer. This reaction introduces the required alcohol stereochemistry found at C-2 of taxol as well as the correct oxidation level at C-1 for introduction of the A-ring carbons.



Conclusions

The [4 + 4] photocycloaddition of four-carbon-tethered pyridones has been found to be sensitive to substitution at the carbons involved in bond formation. Nevertheless, three tetrasubstituted carbons can be simultaneously formed in this reaction.[19] In all cases studied to date, a four-carbon tether yields exclusively trans photoproducts, a phenomenon that may be due to the strain from the tether-derived six-membered ring[36] of the product and possibly coupled with the known thermal chemistry of the cis [4 + 4] products.[17] For the substrates described here, the silyl ether tether substituent fully controls the relative stereochemistry of the product, and the bridged cyclooctane ring can be functionalized with predictable stereoselectively.

(35) Photodimers of 2-pyridones have been reported to revert to the original 2-pyridones thermally (Meyers, A. I.; Singh, P. *J. Org. Chem.* **1970**, *35*, 3022−3030). A pathway for this decomposition could involve retro-aldol of the β-amino carbonyls. Inspection of models suggests that the orbital alignment for this process would be good.

(36) Sieburth, S. McN. *J. Chem. Soc., Chem. Commun.* **1994**, 1663−1664.

(37) Frimer, A. A. *Synthesis* **1977**, 578−579.

Experimental Section[38]

3,*N*-Dimethyl-4-hydroxy-3-methyl-6-[1-(3-hydroxypropyl)]-2-pyridone (21). To a suspension of NaH (0.7 g, 16.7 mmol, 60% in mineral oil, washed with three portions of hexane) in THF (50 mL) at 0 °C was added dropwise ethyl 2-methylacetoacetate (**20**) (2.04 g, 14.1 mmol) followed, after stirring for 10 min, by *n*-butyllithium (1.6 M in hexane, 10 mL, 16 mmol). After a further 10 min, γ-butyrolactone (7.1 mmol, 0.61 g, 0.54 mL) was added dropwise. After a further 15 min, additional *n*-butyllithium (5 mL, 8 mmol) was added, and after a further 30 min, additional γ-butyrolactone (7.1 mmol, 0.61 g, 0.54 mL) was added dropwise. The reaction mixture was then stirred for 0.5 h. After addition of concentrated HCl (6 mL), the solution was extracted with ether (50 mL × 3). The combined organics were dried over Na_2SO_4 and concentrated to give a red oil. Low-boiling components were removed by Kugelrohr distillation (90 °C, 6 mmHg), affording 3.3 g of crude product. This material was used directly in the next reaction.

To a portion of the crude product (0.5 g) was added 40% aqueous methylamine (10 mL), and the resulting mixture was heated to a gentle reflux for 48 h. After cooling, the reaction mixture was neutralized by addition of l0% aqueous HCl and concentrated to give a brown solid. Flash chromatography (1:9 methanol/methylene chloride) gave **21** as colorless crystals (0.27 g, 64% overall): mp 177−178 °C; R_f = 0.27 (1:9 methanol/methylene chloride); ^{1}H NMR (methanol-d_4) δ 6.00 (s, 1H), 3.64 (t, 2H, J = 6.1 Hz), 3.51 (s, 3H), 2.73 (t, 2H, J = 8.7 Hz), 1.92 (s, 3H), 1.81 (m, 2H); ^{13}C NMR (methanol-d_4) δ 167.2, 164.2, 148.8, 106.0, 101.5, 61.7, 31.9, 31.5, 30.5, 9.0; IR (KBr) 3234, 3072, 2922, 1650, 1561, 1415, 1065, 809 cm^{-1}; MS (CI/NH_3) 198 (MH^+, 100), 166 (9), 153 (15), 124 (6), 97 (7); exact mass (CI/NH_3) calcd for $C_{10}H_{16}NO_3$ 198.1130, found 198.1135. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.71; H, 7.61; N, 7.35.

3,*N*-Dimethyl-6-[1-(3-hydroxypropyl)]-4-methoxy-2-pyridone. To a solution of 3,*N*-dimethyl-4-hydroxy-3-methyl-6-[1-(3-hydroxypropyl)]-2-pyridone (**21**) (7.14 g, 0.036 mol) in 200 mL of absolute ethanol was added K_2CO_3 (57 g, 0.41 mol) and the mixture refluxed for 2 h with mechanical stirring. Dimethyl sulfate (19.3 g, 14.5 mL, 0.153 mol) was then added dropwise, and the resulting mixture was refluxed overnight. After cooling, the reaction mixture was filtered, and the residue was washed with methylene chloride. The filtrate was dried over Na_2SO_4 and concentrated to give 11.5 g of a yellow solid. Purification by flash chromatography (1:9 methanol/methylene chloride) gave the product as a colorless solid (6.0 g, 79%): R_f = 0.20 (1:19 methanol/methylene chloride); ^{1}H NMR ($CDCl_3$) δ 5.94 (s, 1H), 3.79 (s, 3H), 3.70 (t, 2H, J = 5.9 Hz), 3.49 (s, 3H), 2.73 (t, 2H, J = 7.5 Hz), 1.95 (s, 3H), 1.84 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 164.9, 163.1, 147.4, 107.2, 94.5, 61.0, 55.5, 31.0, 30.9, 30.4, 8.9; IR (KBr) 3072, 2950, 1648, 1561, 1414, 1158, 1066, 808 cm^{-1}; MS (EI) 211 (M^+, 100), 194 (19), 180 (71), 167 (52), 152 (40), 138 (43); exact mass (EI) calcd for $C_{11}H_{17}NO_3$ 211.1208, found 211.1196. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.49; H, 8.13; N, 6.58.

3,*N*-Dimethyl-6-[1-[3-[(methylsulfonyl)oxy]propyl]]-4-methoxy-2-pyridone. To a 0 °C solution of 3,*N*-dimethyl-6-[1-(3-hydroxypropyl)]-4-methoxy-2-pyridone (0.50 g, 2.3 mmol) and triethylamine (0.80 mL, 5.8 mmol) in methylene chloride (10 mL) was added methanesulfonyl chloride (0.45 mL, 5.8 mmol) dropwise. After stirring at 0 °C for 0.5 h and then at room temperature for 0.5 h, the reaction mixture was poured into 30 mL of a 1:1 mixture of 10% aqueous HCl/saturated NaCl. The aqueous layer was extracted with methylene chloride (30 mL × 3), dried over Na_2SO_4, and concentrated to give 0.783 g of a yellow oil: R_f = 0.41 (1:19 methanol/methylene chloride); ^{1}H NMR ($CDCl_3$) δ 5.94 (s, 1H), 4.28 (t, 2H, J = 5.8 Hz), 3.81 (s, 3H), 3.50 (s, 3H), 3.00 (s, 3H), 2.76 (t, 2H, J = 7.8 Hz), 2.07 (m, 2H), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.8, 162.7, 145.0, 108.0, 95.0, 67.9, 55.6, 37.5, 30.9, 29.8, 27.5, 8.9; IR (film) 3053, 2981, 1644, 1563, 1360, 1263, 1176, 931 cm^{-1}; MS (EI) 289 (M^+, 100), 210 (31), 194 (84), 180 (92), 138 (41), 79 (69); exact mass (EI) calcd for $C_{12}H_{19}NO_5S$ 289.0984, found 289.0989. Anal. Calcd for $C_{12}H_{19}NO_5S$: C, 49.81; H, 6.62; N, 4.84. Found: C, 49.90; H, 6.58; N, 4.78.

3,*N*-Dimethyl-6-[1-(3-iodopropyl)]-4-methoxy-2-pyridone (22). To a solution of 3,*N*-dimethyl-6-[1-[3-[(methylsulfonyl)oxy]propyl]]-4-methoxy-2-pyridone (0.783 g, 2.7 mmol) in dry acetone (75 mL) was added sodium iodide (1.7 g, 11.3 mmol), and the reaction mixture was then heated to a gentle reflux for 1.5 h. After cooling, the mixture was filtered, and the residue was washed with methylene chloride. The filtrate was concentrated and then the residue partitioned between 20 mL of 10% aqueous HCl and 30 mL of methylene chloride. The aqueous layer was extracted with methylene chloride (30 mL × 3); the combined organic layers were dried over Na_2SO_4 and concentrated to give **22** as light yellow crystals (0.745 g, 98%): mp 81−82 °C; R_f = 0.46 (1:19 methanol/methylene chloride); ^{1}H NMR ($CDCl_3$) δ 5.96 (s, 1H), 3.82 (s, 3H), 3.52 (s, 3H), 3.23 (t, 2H, J = 6.4 Hz), 2.77 (t, 2H, J = 7.7 Hz), 2.09 (m, 2H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.7, 162.5, 145.1, 107.9, 94.8, 55.5, 34.4, 31.05, 31.0, 8.9, 4.7; IR (film) 3048, 2979, 1643, 1563, 1400, 1236, 1179, 795 cm^{-1}; MS (EI) 321 (M^+, 100), 194 (62), 166 (28), 138 (24); exact mass (EI) calcd for $C_{11}H_{16}INO_2$ 321.0226, found 321.0220. Anal. Calcd for $C_{11}H_{16}INO_2$: C, 41.14; H, 5.02; N, 4.36. Found: C, 41.00; H, 4.98; N, 4.28.

2-Chloro-α-hydroxy-3-pyridineacetonitrile. To a 0 °C solution of NaCN (6.0 g, 122.4 mmol) in 120 mL of water was added 2-chloronicotinaldehyde[39] (10.0 g, 70.6 mmol) followed by glacial acetic acid (6.9 mL, 120 mmol), resulting in the formation of a white precipitate. After stirring for 23 h, the reaction mixture was warmed to room temperature. The mixture was filtered, and the residue was washed with 150 mL of water to give colorless crystals. After saturating the aqueous layer with NaCl, it was extracted with chloroform (100 mL × 3). The organic layer was dried over Na_2SO_4 and concentrated to give colorless crystals (the combined product weight was 11.6 g, 98%): R_f = 0.16 (1:49 methanol/methylene chloride); ^{1}H NMR (methanol-d_4) δ 8.4 (dd, 1H, J = 1.8, 4.8 Hz), 8.1 (dd, 1H, J = 1.8, 7.8 Hz), 7.5 (dd, 1H, J = 4.8, 7.8 Hz), 5.82 (s, 1H); ^{13}C NMR (methanol-d_4) δ 150.1, 148.1, 137.3, 131.1, 123.8, 118.6, 59.2; IR (film) 3115, 2853, 2693, 1660, 1575, 1458, 1411, 1260 cm^{-1}.

2-Chloro-α-(1-ethoxyethoxy)-3-pyridineacetonitrile (23). To a solution of (2-chloro-3-pyridinyl)hydroxyacetonitrile (5.0 g, 29.8 mmol) in 150 mL of THF was added *p*-toluenesulfonic acid (0.29 g, 1.5 mmol) at 0 °C. Freshly distilled ethyl vinyl ether (7.1 mL, 74.2 mmol) was added by syringe pump over 15 min and allowed to stir overnight. After addition of 100 mL of saturated NH_4Cl solution, the aqueous layer was extracted with methylene chloride (70 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated to give a brown oil (7.07 g). Kugelrohr

(38) For general experimental procedures, see ref 17.

(39) Brewster, K.; Harrison, J. M.; Inch, T. D. *J. Heterocycl. Chem.* **1978**, *15*, 1497−1499.

(40) Clark, M.; Cramer, R. D., III; Van Opdenbosch, N. *J. Comput. Chem.* **1989**, *10*, 982−1012.

distillation at 90 °C (1.5 mmHg) gave **23** as a light yellow oil and as a 1:1 mixture of diastereomers (5.91 g, 96%): $R_f = 0.21$, 0.26 (1:5 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$) δ 8.43 (dd, 1H, J = 1.8, 4.8 Hz), 8.03 (dd, 1H, J =1.8, 7.7 Hz), 7.36 (dd, 1H, J = 4.8, 7.7 Hz), 5.79 (s, 0.5H), 5.67 (s, 0.5H), 5.13 (q, 0.5H, J = 5.4 Hz), 5.01 (q, 0.5H, J = 5.4 Hz), 3.72 (m, 0.5H), 3.56 (m, 1.5H), 1.47 (d, 1.5H, J = 5.4 Hz), 1.40 (d, 1.5H, J = 5.4 Hz), 1.21 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 150.5, 149.4, 137.6, 129.4, 123.0, 116.3, 101.2, 99.7, 61.7, 19.5, 14.9; IR (neat) 3055, 2981, 2933, 1568, 1411, 1145, 1078, 1046, 952, 800, 749 cm^{-1}; MS (CI/NH_3) 241 (MH^+, 100), 192 (15), 129 (25), 88 (71), 71 (46); exact mass (CI/NH_3) calcd for $C_{11}H_{14}ClN_2O_2$ 241.0744, found 241.0743. Anal. Calcd for $C_{11}H_{13}ClN_2O_2$: C, 54.89; H, 5.44; N, 11.64. Found: C, 54.94; H, 5.43; N, 11.56.

6-[4-(2-Chloro-3-pyridinyl)-4-oxobutyl]-4-methoxy-1,3-dimethyl-2(1*H*)-pyridinone (24). To a −78 °C solution of NaHMDS (0.5 M in THF, 16.2 mL, 8.16 mmol) was added dropwise over 12 min a solution of nitrile **23** (1.87 g, 7.77 mmol) in freshly distilled DMPU (16 mL). After stirring for 35 min at this temperature, a solution of pyridone **22** (1.0 g, 3.1 mmol) in THF (16 mL) was added dropwise over 5 min, and the reaction mixture was allowed to warm to room temperature over 10 h. After addition of saturated NH_4Cl (50 mL), the aqueous layer was extracted with ethyl acetate (50 mL × 3); the combined organic layers were dried over Na_2SO_4 and concentrated to give a brown oil (12.6 g). The excess **23** and DMPU were removed by Kugelrohr distillation at 110 °C (2.0 mmHg). The remaining brown oil (1.5 g) was taken up in a solution of 5% H_2SO_4 in methanol (v/v, 20 mL) and stirred for 1 h at room temperature. The mixture was concentrated *in vacuo* and then partitioned between 50 mL of water and 50 mL of ethyl acetate. The organic layer was mixed with 50 mL of 0.5 N NaOH and shaken for 10 min. After extraction of the aqueous layer with methylene chloride (50 mL × 3), the combined organic layers were dried over Na_2SO_4 and concentrated to give 1.3 g of brown oil. Purification by flash chromatography (3:97 methanol/methylene chloride) gave **24** as a light brown gum (0.718 g, 69%): $R_f = 0.32$ (3:97 methanol/methylene chloride); ^{1}H NMR ($CDCl_3$) δ 8.50 (dd, 1H, J = 1.8, 4.8 Hz), 7.80 (dd, 1H, J = 1.8, 7.6 Hz), 7.34 (dd, 1H, J = 4.8, 7.6 Hz), 5.90 (s, 1H), 3.78 (s, 3H), 3.55 (s, 3H), 3.11 (t, 2H, J = 6.7 Hz), 2.71 (t, 2H, J = 7.4 Hz), 2.07 (m, 2H), 1.97 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 200.5, 164.8, 162.7, 151.5, 147.3, 146.3, 138.1, 135.2, 122.7, 107.9, 94.7, 55.6, 41.5, 33.2, 31.1, 22.3, 9.0; IR (film) 3049, 2978, 1639, 1560, 1397, 1297, 1279, 1173, 1076, 806 cm^{-1}; MS (EI) 334 (100, M^+), 194 (63), 180 (69), 167 (41), 138 (37), 112 (22); exact mass (EI) calcd for $C_{17}H_{19}ClN_2O_3$ 334.1084, found 334.1093.

6-[4-(2-Chloro-3-pyridinyl)-4-(hydroxyimino)butyl]-4-methoxy-1,3-dimethyl-2(1*H*)-pyridinone (25). To a solution of ketone **24** (1.4 g, 4.18 mmol) in pyridine (30 mL) was added a solution of hydroxylamine hydrochloride (0.40 g, 6.2 mmol) in water (5 mL), and the resulting mixture was heated to a gentle reflux for 3 h. After cooling, the mixture was poured into 3% aqueous HCl (150 mL) and extracted with ethyl acetate; the combined organics were dried over $MgSO_4$ and concentrated to give oxime **25** as a yellow solid (1.1 g, 75%), a 1:1 mixture of *E* and *Z* isomers: R_f = 0.34 (1:9 methanol/methylene chloride); ^{1}H NMR (DMSO-d_6) δ 11.6 (s, 0.5H), 11.0 (s, 0.5H), 8.3 (m, 1H), 7.8 (m, 0.5H), 7.7 (m, 0.5H), 7.4 (m, 1H), 6.1 (s, 0.5H), 6.08 (s, 0.5H), 3.74 (s, 1.5H), 3.72 (s, 1.5H), 3.31 (s, 1.5H), 3.29 (s, 1.5H), 2.75 (m, 2H), 2.63 (m, 2H), 1.77 (s, 1.5H), 1.76 (s, 1.5H), 1.6 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 164.0, 162.9, 155.9, 152.6, 150.0, 149.8, 148.8, 148.2, 147.9, 147.1, 140.5, 139.1, 132.9, 131.6, 123.6, 123.4, 105.4, 94.3, 94.2, 56.0, 33.7, 33.1, 32.8, 30.9, 30.7, 27.7, 24.5, 23.7, 9.5; MS (EI) 349 (4, M^+), 332 (4), 314 (3), 194 (5), 180 (33), 167 (26), 78 (62), 63 (100).

3-[3-(1,2-Dihydro-1,3-dimethyl-4-methoxy-2-oxo-6(1*H*)-pyridinyl)-1-propyl]isoxazolo[5,4-*b*]pyridine (26). To a 0 °C suspension of NaH (500 mg, 12.5 mmol, 60% in mineral oil, washed with three portions of hexane) in pyridine (75 mL) was added oxime **25** (1.10 g, 3.13 mmol) in pyridine (7 mL) over a period of 10 min. The mixture was allowed to warm to room temperature over 1 h and then heated to 60 °C for 4 h. The reaction mixture was poured into 10% aqueous HCl (200 mL) and extracted with three 75 mL portions of chloroform. Concentration of the combined organics gave a yellow solid (911 mg). Flash chromatography over silica gel (1:9 methanol/methylene chloride) gave **26** as an oil (822 mg, 83%): R_f = 0.52 (1:9 methanol/methylene chloride); ^{1}H NMR ($CDCl_3$) δ 8.6 (dd, 1H, J = 7.8, 1.8 Hz), 8.0 (dd, 1H, J = 4.5, 1.8 Hz), 7.3 (dd, 1H, J = 7.8, 4.5 Hz), 5.92 (s, 1H), 3.79 (s, 3H), 3.52 (s, 3H), 3.2 (t, 2H, J = 6 Hz), 2.7 (t, 2H, J = 7.5 Hz), 2.2 (m, 2H), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.7, 164.8, 162.6, 157.9, 150.8, 145.8, 131.0, 119.5, 112.7, 107.7, 94.9, 55.6, 33.1, 31.0, 25.0, 8.9.

6-[4-(1,2-Dihydro-1-methyl-2-oxo-3-pyridinyl)-4-hydroxybutyl]-4-methoxy-1,3-dimethyl-2(1*H*)-pyridinone (27) from 26. To a solution of **26** (86 mg, 0.27 mmol) and H_3BO_3 (51 mg, 0.82 mmol) in methanol/water (5:1, 6 mL) was added Raney nickel (3 drops of a commercial 50% aqueous slurry), and the mixture was stirred under 1 atm of hydrogen for 6 h. Filtration and concentration *in vacuo* gave a yellow solid (753 mg). Flash chromatography over silica gel (gradient of 2−10% methanol in methylene chloride) gave 1,3-dimethyl-4-methoxy-6-[4-[1-oxo-1-(1,2-dihydro-2-oxo-3-pyridinyl)butyl]]-2(1*H*)-pyridone as a colorless solid (50 mg, 58%): R_f = 0.35 (1:9 methanol/methylene chloride); ^{1}H NMR ($CDCl_3$) δ 8.2 (dd, 1H, J = 7.2, 2.1 Hz), 7.6 (dd, 1H, J = 6.3, 2.1 Hz), 6.4 (dd, 1H, J = 7.2, 6.3 Hz), 5.98 (s, 1H), 3.8 (s, 3H), 3.5 (s, 3H), 3.2 (t, 2H, J = 6 Hz), 2.6 (t, 2H, J = 7.5 Hz), 2.0 (m, 2H), 1.98 (s, 3H); ^{13}C NMR (methanol-d_4) δ 198.7, 165.1, 163.2, 147.4, 145.1, 140.3, 138.2 107.5, 106.6, 95.3, 95.1, 55.6, 41.7, 33.5, 31.3, 22.4, 8.9.

To a 0 °C solution of 1,3-dimethyl-4-methoxy-6-[4-[1-oxo-1-(1,2-dihydro-2-oxo-3-pyridinyl)butyl]]-2(1*H*)-pyridone (164 mg, 0.52 mmol) in ethanol (15 mL) was added $NaBH_4$ (25 mg, 0.66 mmol). The mixture was allowed to warm to room temperature over 4 h, filtered through silica gel, and concentrated to give 1,3-dimethyl-4-methoxy-6-[4-[1-hydroxy-1-(1,2-dihydro-2-oxo-3-pyridinyl)butyl]]-2(1*H*)-pyridone as a pale yellow solid (100 mg, 61%): mp 192−193 °C; R_f = 0.18 (1:9 methanol/methylene chloride); ^{1}H NMR (methanol-d_4) δ 7.6 (d, 1H, J = 6.3 Hz), 7.3 (d, 1H, J = 6.6 Hz), 6.4 (t, 1H, J = 6.9 Hz), 6.2 (s, 1H), 3.8 (s, 3H), 3.5 (s, 3H), 2.7 (m, 2H), 1.92 (s, 3H), 1.8−1.6 (m, 4H); ^{13}C NMR (methanol-d_4) δ 165.0, 164.4, 162.0, 148.9, 136.6, 135.5, 132.7, 106.9, 106.3, 95.6, 67.6, 55.1, 35.4, 33.0, 30.5, 24.0, 7.7; MS (EI) 318 (12, MH^+), 300 (8), 194 (21), 180 (100).

To a solution of 1,3-dimethyl-4-methoxy-6-[4-[1-hydroxy-1-(1,2-dihydro-2-oxo-3-pyridinyl)butyl]]-2(1*H*)-pyridone (100 mg, 0.314 mmol) in methanol (7 mL) were added iodomethane (446 mg, 3.14 mmol) and anhydrous K_2CO_3 (174 mg, 1.26 mmol). The mixture was stirred at room temperature for 16 h and then filtered through Celite. Concentration *in vacuo* and silica gel chromatography (1:9 methanol/methylene chloride) gave 55 mg of **27** (53%) as an oil.

3-[4-(1,6-Dihydro-1,5-dimethyl-4-methoxy-6-oxo-2-pyridinyl)-1-oxobutyl]-1-methyl-2-pyridone. To a solution of 6-[4-[1-(2-chloro-3-pyridinyl)-1-oxobutyl]]-1,3-dimethyl-4-methoxy-

2-pyridone (**24**) (31.5 mg, 0.0941 mmol) in methylene chloride (5 mL) was added Me_3OBF_4 (33.8 mg, 0.229 mmol), and the suspension was refluxed for 5 h. Removal of the solvent left a light white salt. Glacial acetic acid (6 μL, 0.104 mmol), ethanol (6 μL, 0.104 mmol), and triethylamine (0.036 mL, 0.259 mmol) were added to the suspension of the pyridinium salt in 5 mL of methylene chloride. The reaction mixture was refluxed for 12 h. The solvent was removed, and the residue was partitioned between 10 mL of 0.1 N HCl and 15 mL of methylene chloride; the aqueous layer was then extracted with methylene chloride (10 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$, dried over $NaSO_4$, and concentrated to give a yellow solid. Chromatography (3:97 methanol/methylene chloride) gave the product as colorless crystals (24.2 mg, 78%): mp 154 −155 °C; R_f = 0.49 (1:19 methanol/methylene chloride); ^{1}H NMR ($CDCl_3$) δ 8.14 (dd, 1H, J = 2.1, 7.2 Hz), 7.61 (dd, 1H, J = 2.1, 6.5 Hz), 6.29 (t, 1H, J = 6.9 Hz), 5.87 (s, 1H), 3.80 (s, 3H), 3.60 (s, 3H), 3.54 (s, 3H), 3.27 (t, 2H, J = 6.9 Hz), 2.66 (t, 2H, J = 8.2 Hz), 2.03 (m, 2H), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 198.9, 165.0, 163.0, 161.4, 147.4, 143.6, 143.4, 127.6, 107.9, 105.4, 94.7, 55.7, 41.8, 38.1, 33.6, 31.1, 22.8, 8.9; IR (film) 3053, 2979, 1675, 1642, 1543, 1292, 1179, 1110, 998 cm^{-1}; MS (EI) 330 (M$^+$, 27), 274 (30), 194 (13), 180 (100), 164 (20), 136 (28); exact mass (EI) calcd for $C_{18}H_{22}N_2O_4$ 330.1580, found 330.1571.

6-[4-(1,2-Dihydro-1-methyl-2-oxo-3-pyridinyl)-4-hydroxybutyl]-4-methoxy-1,3-dimethyl-2(1*H*)-pyridinone (27). To a 0 °C solution of 3-[4-(1,6-dihydro-1,5-dimethyl-4-methoxy-6-oxo-2-pyridinyl)-1-oxobutyl]-1-methyl-2-pyridone (300 mg, 0.91 mmol) in ethanol (10 mL) was added $NaBH_4$ (34 mg, 0.92 mmol), and after 20 min the mixture was warmed to room temperature for 2 h. Ethanol was removed under reduced pressure and the residue was partitioned between 10 mL of water and 10 mL of methylene chloride. The aqueous layer was acidified to pH 5−6 by 0.1 N HCl, extracted with methylene chloride, dried over Na_2SO_4, and concentrated to give a yellow solid. Chromatography with 5:95 methanol/methylene chloride gave a light yellow solid (0.262 g, 89%): mp 166−167 °C; R_f = 0.48 (1:9 methanol/methylene chloride); ^{1}H NMR ($CDCl_3$) δ 7.28 (dd, 1H, J = 1.8, 6.8 Hz), 7.24 (dd, 1H, J =1.8, 6.8 Hz), 6.19 (t, 1H, J = 6.8 Hz), 5.87 (s, 1H), 4.62 (m, 2H), 3.79 (s, 3H), 3.54 (s, 3H), 3.47 (s, 3H), 2.64 (m, 2H), 1.95 (s, 3H), 1.84 (m, 3H), 1.72 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 165.0, 163.0, 162.5, 147.4, 136.8, 134.8, 134.2, 107.8, 107.8, 94.6, 71.5, 55.6, 37.1, 35.4, 33.8, 30.8, 24.6, 8.9; IR (film) 3382, 2944, 1644, 1557, 1463, 1401, 1235, 1176, 1110, 763, 733 cm^{-1}.

6-[4-(1,2-Dihydro-1-methyl-2-oxo-3-pyridinyl)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]butyl]-4-methoxy-1,3-dimethyl-2(1*H*)-pyridinone (28). To a solution of 3-[4-(1,6-dihydro-1,5-dimethyl-4-methoxy-6-oxo-2-pyridinyl)-1-hydroxybutyl]-1-methyl-2-pyridone (**27**) (0.225 g, 0.678 mmol) in DMF (10 mL) were added *tert*-butyldimethylchlorosilane (0.511 g, 3.39 mmol) and imidazole (0.462 g, 6.78 mmol). After stirring for 4 h at room temperature, the reaction mixture was partitioned between 60 mL of ether and 60 mL of water. The aqueous layer was extracted with ether (60 mL × 4); the combined ether extracts were washed with brine, dried over $NaSO_4$, and concentrated to give 0.334 g of a colorless oil. Chromatography (1:19 methanol/methylene chloride) gave **28** as a colorless oil (0.287 g, 95%): R_f = 0.42 (1:19 methanol/methylene chloride); ^{1}H NMR ($CDCl_3$) δ 7.45 (dd, 1H, J = 1.6, 6.8 Hz), 7.19 (dd, 1H, J = 1.6, 6.8 Hz), 6.19 (t, 1H, J = 6.8 Hz), 5.88 (s, 1H), 4.96 (t, 1H, J = 5.8 Hz), 3.79 (s, 3H), 3.53 (s, 3H), 3.45 (s, 3H), 2.55 (m, 2H), 1.95 (s, 3H), 1.65 (m, 4H), 0.89 (s, 9H), 0.054 (s, 3H), 0.027 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.9, 162.9, 161.3, 147.4, 136.2, 135.8, 134.6, 107.6, 105.3, 94.4, 68.8, 55.5, 37.2, 36.5, 33.9, 30.8, 25.8, 23.7, 18.1, 8.8, −4.7, −5.0; IR (film) 3051, 2955, 1646, 1593, 1560, 1098, 838 cm^{-1}; MS (EI) 446 (M$^+$, 84), 389 (100), 314 (32), 179 (61), 148 (33), 75 (51); exact mass (EI) calcd for $C_{24}H_{38}N_2O_4Si$ 446.2601, found 446.2607. Anal. Calcd for $C_{24}H_{38}N_2O_4Si$: C, 64.59; H, 8.58; N, 6.28. Found: C, 64.47; H, 8.61; N, 6.23.

(3α,4*β*,6a*β*,7*β*,10aα)-(±)-7-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]butyl]-4,5,7,8,9,10-hexahydro-12-methoxy-1,3,5-trimethyl-3,10a:4,6a-dietheno-1,5-benzodiazocine-2,6(1*H*,3*H*)-dione (29). A stream of dry nitrogen was bubbled for 5 min through a methanol (5 mL) solution of **28** (104 mg, 0.233 mmol, 0.05 M) in a quartz test tube. This solution was irradiated for 39 h using a 450 W medium-pressure mercury lamp fitted with a water-cooled quartz jacket and a Pyrex filter and then concentrated to yield 109 mg of a colorless solid: R_f = 0.79 (1:19 methanol/methylene chloride); ^{1}H NMR ($CDCl_3$) δ 6.45 (dd, 1H, J = 6.6, 8.7 Hz), 6.30 (dd, 1H, J = 1.2, 8.7 Hz), 5.17 (s, 1H), 4.24 (t, 1H, J = 4.2 Hz), 3.52 (s, 3H), 3.39 (dd, 1H, J = 6.6, 1.2 Hz), 2.88 (s, 3H), 2.84 (s, 3H), 2.59 (m, 2H), 1.87 (m, 2H), 1.75 (m, 2H), 1.45 (s, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (methanol-d_4) δ 178.2, 176.7, 161.1, 134.9, 132.8, 106.3, 70.2, 68.2, 64.3, 63.2, 55.8, 55.6, 34.4, 31.4, 31.1, 26.9, 26.1, 19.4, 18.6, 17.1, −4.9, −4.4; IR (film) 3041, 2944, 1738, 1646, 1463, 1386, 1104, 1061, 837 cm^{-1}; MS (EI) 446 (M$^+$, 52), 389 (100), 208 (16), 195 (38), 179 (78), 148 (19), 73 (31); exact mass (EI) calcd for $C_{24}H_{38}N_2O_4Si$ 446.2601, found 446.2602.

(3α,4*β*,6a*β*,7*β*,10aα)-(±)-7-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4,5,7,8,9,10,13,14-octahydro-12-methoxy-1,3,5-trimethyl-3,10a:4,6a-dietheno-1,5-benzodiazocine-2,6(1*H*,3*H*)-dione (30). To a solution of photoproduct **29** (107 mg, 0.24 mmol) in methanol (2 mL) was added PtO_2 (20 mg), and the mixture was stirred under 1 atm of hydrogen at ambient temperature for 5 h. Filtration through Celite and concentration gave 105 mg of a light yellow oil. Flash chromatography over silica gel (3:97 methanol/methylene chloride) gave **30** as a colorless solid (70 mg, 66.4%, two steps): mp 174−175 °C; R_f = 0.88 (1:9 methanol/methylene chloride); ^{1}H NMR ($CDCl_3$) δ 5.17 (s, 1H), 4.08 (t, 1H, J = 2.6 Hz), 3.52 (s, 3H), 3.30 (d, 1H, J = 6.6 Hz), 3.03 (s, 3H), 2.82 (s, 3H), 2.69 (m, 2H), 2.05 (m, 2H), 1.79 (m, 4H), 1.48 (m, 2H), 1.24 (s, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (methanol-d_4) δ 175.0, 174.1, 157.6, 100.9, 74.1, 67.8, 60.1, 58.1, 55.2, 52.8, 35.1, 30.2, 29.7, 28.3, 26.2, 25.9, 23.6, 19.8, 18.0, 14.7, −4.5, −4.8; IR (film) 3085, 2952, 1670, 1648, 1459, 1254, 1052, 836 cm^{-1}; MS (EI) 448 (M$^+$, 74), 391 (85), 339 (30), 316 (41), 254 (34), 194 (37), 181 (96), 167 (100), 75 (87); exact mass (EI) calcd for $C_{24}H_{40}N_2O_4Si$ 448.2757, found 448.2756. Anal. Calcd for $C_{24}H_{40}N_2O_4Si$: C, 64.25; H, 8.99; N, 6.24. Found: C, 64.30; H, 8.94; N, 6.20.

(3α,4*β*,6a*β*,7*β*,10aα,11*β*)-4,5,7,8,9,10,11,12,13,14-Decahydro-12,12-dimethoxy-7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-11-hydroxy-1,3,5-trimethyl-3,10a:4,6a-dietheno-1,5-benzodiazocine-2,6(1*H*, 3*H*)-dione (31). To a 0 °C solution of **30** (34 mg, 0.076 mmol) in methanol (2 mL) was added MCPBA (85%, 46.2 mg, 0.228 mmol), and the reaction mixture was allowed to warm to room temperature overnight. The mixture was concentrated *in vacuo*, and the residue was partitioned between 5 mL of saturated $NaHCO_3$ and 10 mL of $CHCl_3$. The aqueous layer was extracted with $CHCl_3$ (10 mL × 3); the combined organic layers were dried over Na_2SO_4 and concentrated to give 36 mg of a yellow solid. Column chromatography over silica gel (2:98 methanol/methylene chloride) gave **31** as a colorless solid (29.4 mg, 78%): mp 158−160 °C; R_f = 0.72

(1:9 methanol/methylene chloride); ^{1}H NMR ($CDCl_3$) δ 4.08 (m, 2H), 4.06 (s, 1H), 3.45 (s, 3H), 3.43 (s, 3H), 3.14 (d, 1H, J = 6.3 Hz), 3.01 (s, 3H), 2.98 (s, 3H), 2.63 (m, 2H), 2.05 (m, 2H), 1.85−1.65 (m, 6H), 1.36 (s, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.0, 173.8, 102.8, 75.1, 73.8, 66.0, 64.6, 57.8, 56.2, 52.4, 52.2, 36.4, 30.6, 29.8, 27.6, 25.9, 22.6, 21.7, 18.0, 15.1, 13.6, −4.4, −4.8; MS (EI) 496 (M^+, 4), 465 (13), 439 (57), 407 (95), 337 (21), 254 (20), 205 (37), 129 (24), 73 (100); exact mass (EI) calcd for $C_{25}H_{44}N_2O_6Si$ 496.2969, found 496.2985. Anal. Calcd for $C_{25}H_{44}N_2O_6Si$: C, 60.50; H, 8.94; N, 5.65. Found: C, 60.27; H, 9.07; N, 5.54.

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Supporting Information Available: Proton and carbon NMR spectra for **21**−**31** and intermediates (24 pages). See any current masthead page for ordering and Internet access instructions.

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