Selective Intermolecular Photo-[4 + 4]-cycloaddition with 2-Pyridone Mixtures. 2. Preparation of (1α,2*β*,5*β*,6α)-3-Butyl-9-methoxy-3,7-diazatricyclo[4.2.2.2^{2,5}]dodeca-9,11-diene-4,8-dione

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Photochemistry of 2-pyridone mixtures can be selective and thereby lead to useful quantities of [4 + 4] cycloaddition cross products. The selective intermolecular reaction described here employs an excess of 4-methoxy-2-pyridone (**6**), which does not photodimerize but will undergo [4 + 4] cycloaddition with 2-pyridones without a 4-methoxy group such as *N*-butyl-2-pyridone **12**. Isolated yields of the trans product (1α,2*β*,5*β*,6α)-3-butyl-9-methoxy-3,7-diazatricyclo[4.2.2.2^{2,5}]dodeca-9,-11-diene-4,8-dione (**7**) are very sensitive to the ratio of the two starting pyridones, and this product has been isolated in yields of up to 51%. This photoreaction produces, in a single step from simple aromatic precursors, a tricyclic product with four stereogenic centers and four distinct functional groups.

Cycloaddition reactions are regarded as one of the most powerful synthetic methods because they form multiple bonds and multiple stereogenic centers in a single step. This analysis is generally true because cycloaddition reactions are also closely associated with stereo and regioselectivity, the classic example being the Diels−Alder reaction.[1] A third, but less frequently discussed, selectivity is the selection of two reacting species *for each other* rather than for themselves. Once again, the Diels−Alder reaction provides outstanding examples of diene/dienophile cycloadditions with dimerization at most a minor diversion. Electronically tuned reaction partners play a significant role here; an electron rich diene is best coupled with an electron poor dienophile, and under these circumstances the highest levels of selectivity are found.

Higher-order cycloadditions[2,3] are less well studied; however, they can and do profit from the same selectivities. Photocycloaddition of 2-pyridone **2**, originally reported by Taylor and Paudler,[4] has a native regioselectivity for head-to-tail products and a stereoselectivity favoring the trans isomers **3** (Figure 1).[5] The third selectivity, however, is missing: nearly all of the known 2-pyridone photocycloadditions are *dimerizations*, producing a symmetric product with a center of inversion.[6] In contrast, most potential synthetic targets are asymmetric, including most natural products. Our studies of 2-pyridone [4 + 4] cycloaddition initially focused on an intramolecular variation in which two different pyridones were tethered at the 3- and 6′-positions to reinforce their normal head-to-tail regioselectivity.[7] As part of this investigation, we considered the photochemistry of 4-alkoxy-2-pyridone with a 4-unsubstituted-2-pyridone (**4**) and elected to investigate this reaction in an untethered, intermolecular form to ensure that such a cycloaddition was possible, before undertaking an intramolecular application with **4**.[8]

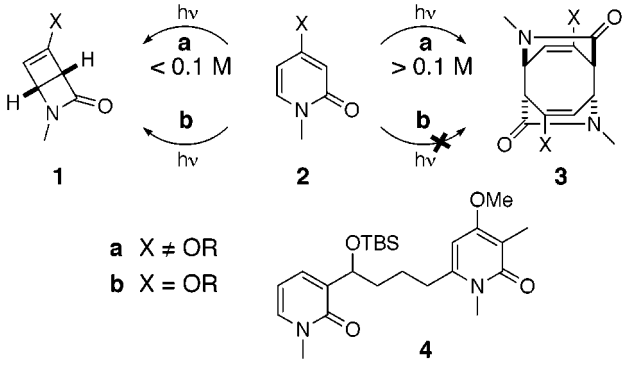

Figure 1. Presence of a 4-alkoxy group (X = OR) prevents photodimerization to **3**, but not isomerization to **1** or intramolecular photocycloaddition of **4**.

The presence of a 4-alkoxy group on the 2-pyridone perturbs the photochemistry of this molecule. Photo-[4 + 4] dimerization to give **3a** is the major photochemical pathway for 2-pyridones **2a**, except under dilute conditions where unimolecular isomerization to give Dewar pyridone **1a** dominates.[9] In contrast, the presence of a 4-alkoxy group (**2b**) shuts down the [4 + 4] pathway, leading to **1b** as the only observed transformation. This photochemical behavior was first observed by Schleigh and De Selms for the natural product ricinine[10] and was

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(6) Photo-[4 + 4]-cycloaddition of 2-pyridones in a mixture with other 1,3-dienes have been reported. In all cases dimerization of the pyridone competes with cross reaction, and an excess of the other substrate is used. Triazolo[1,5-*a*]pyridines: Nagano, T.; Hirobe, M.; Okamoto, T. *Tetrahedron Lett.* **1977**, 3891−3894. 1,3-Dienes: see ref 22.

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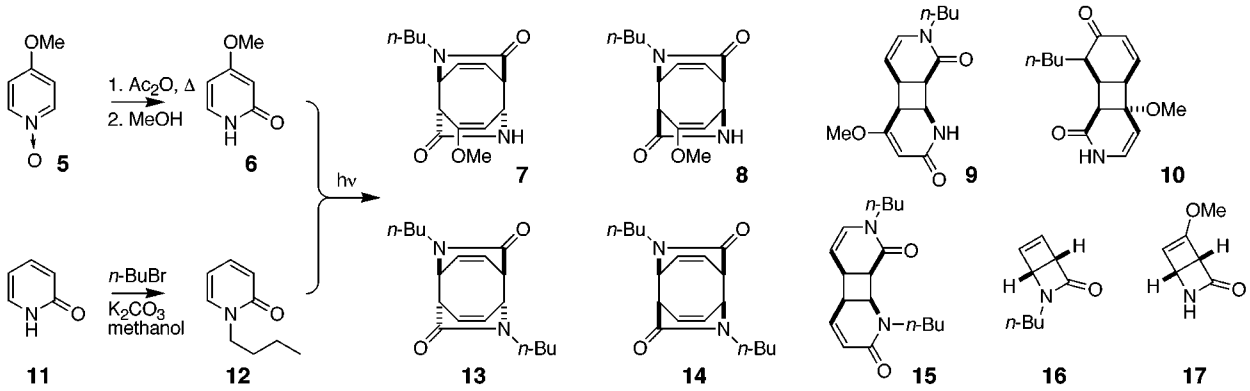

Figure 2. Photoproducts from a mixture of **6** and **12**.

generalized by Kaneko who employed Dewar pyridones **1b** in the synthesis of novel β-lactams.[11] While the reasons that **2b** resists photodimerization remain obscure, we needed to know, for the purposes of intramolecular photochemistry with **4**, if a 4-alkoxy group would allow [4 + 4] reactions with other 2-pyridones. The photochemistry of bis-2-pyridone **4** was studied as a synthetic route to the anticancer drug paclitaxel[12] and its analogues. Successful photocycloaddition of **4** led to a [4 + 4] product with one alkene an enol ether.[13] The position of this enol ether methoxy group allows for introduction of paclitaxel's A-ring carbons.[14]

Results and Discussion

To study the intermolecular reaction of a 2-pyridone mixture, we elected to use 4-methoxy-2-pyridone **6** and *N*-butyl-2-pyridone **12**, both of which were available in a single operation from commercially available reagents (Figure 2). Pyridone **12** was chosen because its dimers are known, and its dimerization/isomerization (**13** vs **16**) reactivity was found by Nakamura to be identical to *N*-methyl-2-pyridone, the simplest *N*-alkyl-2-pyridone.[9] Further, the *N*-butyl group was anticipated to make the photoproducts lipophilic and easily handled. To contrast with **12**, an *N*-unsubstituted **6** was chosen to allow for its facile separation from the photoreaction mixture by simple base extraction of this phenol-like substance. Methoxypyridone **6** was prepared by rearrangement of 4-methoxypyridine *N*-oxide **5** with refluxing acetic anhydride. The resulting 2-acetoxy-4-methoxypyridine was then directly hydrolyzed by refluxing with methanol.[15,16] *N*-Butyl-2-pyridone **12** has been prepared by alkylation of the sodium salt of 2-pyridone with bromobutane, yielding a 6:1 mixture of *N*- and *O*-alkylation in ethanol (42% yield overall).[17] As with many of our 2-pyridones,[18] we found the potassium salt in methanol to be more selective for *N*-alkylation, giving an 80% yield of **12**.

For the initial reaction, a 1:1 solution of 4-methoxy-2-pyridone and *N*-butyl-2-pyridone in methanol, both at 0.25 M, was irradiated. The initial concentration of pyridones was considered to be critical because at concentrations below 0.1 M isomerization of **12** to Dewar pyridone **16** becomes significant.[9] In the event, the mixture of **6** and **12** was irradiated for 72 h with a standard 450 W medium-pressure mercury lamp fitted with a Pyrex filter. The resulting mixture of products, still containing both starting reagents, was concentrated and separated chromatographically. A pair of products **7** and **8** were identified as the trans and cis isomers of the desired [4 + 4] cycloaddition between **6** and **12**.[19] The identity of the trans cross-product **7** was subsequently confirmed by X-ray crystallography.[8] This result provided the necessary preliminary support for the intramolecular photochemistry of **4** that has been reported elsewhere.[13]

In addition to the two cross products **7** and **8**, the two known dimers **13** and **14** were isolated, as well as the cyclobutane **15** which presumably results from Cope rearrangement of the cis [4 + 4] product **14**.[8,9] The cyclooctadiene in **14** can only rearrange to one product **15** because of **14**'s C_2 axis of symmetry. Rearrangement of cis cross-product **8**, which lacks symmetry, leads to two different cyclobutanes, **9** and **10**. We were surprised, however, to find very little Dewar pyridone **16**, derived from **12**, and none from the 4-methoxy-2-pyridone substrate **6** (see Table 1).[20]

The major product, trans dimer **13**, was favored over the desired trans cross-product **7** by nearly a factor of 2, and both were formed in poor yield (22% and 6%, respectively, based on **12**). These yields, combined with

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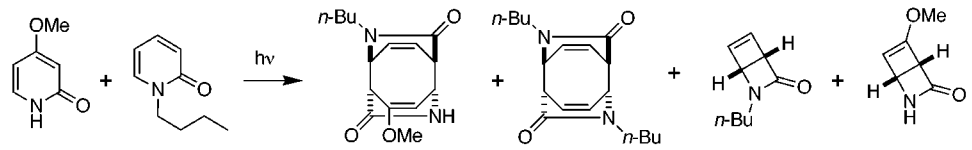
(18) Sieburth, S. McN.; Hiel, G.; Lin, C.-H.; Kuan, D. P. *J. Org. Chem.* **1994**, *59*, 80−87. See ref 28.

(19) The first reaction of a 2-pyridone mixture using 4-methoxy-2-pyridone was performed with *N*-methyl-2-pyridone; however, only qualitative data not directly comparable to that presented here was obtained. See: K. Ravindran, Ph.D. Thesis, SUNY at Stony Brook, 1994.

(20) Absence of significant amounts of **17** may be due to the dominance of the pyridone **12** chromophore (see Figure 3). Alternatively, absence of **17** could be caused by our use of a medium-pressure mercury lamp, with its limited spectral output, rather than a high-pressure mercury lamp[11] with its relatively homogeneous spectral dispersion. See Horspool, W. M. In *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum: New York, 1984; pp 489−509. Murov, S. L.; Carmichael, I.; Hug, G. L. *Handbook of Photochemistry*; Marcel Dekker: New York, 1993.

Table 1.



entry	molar ratio (% recovery) 6		12	7	molar ratio	13	isolated yields 16	17
1	(97)	**1 : 1**	(45)	6	**1 : 1.8**	22	2	0
2	(90)	**4 : 1**	(0)	42	**7.2 : 1**	12	1	0
3	(90)	**7 : 1**	(0)	51	**13 : 1**	8	5	0
4	(94)	**9 : 1**	(7)	47	**16 : 1**	6	7	2

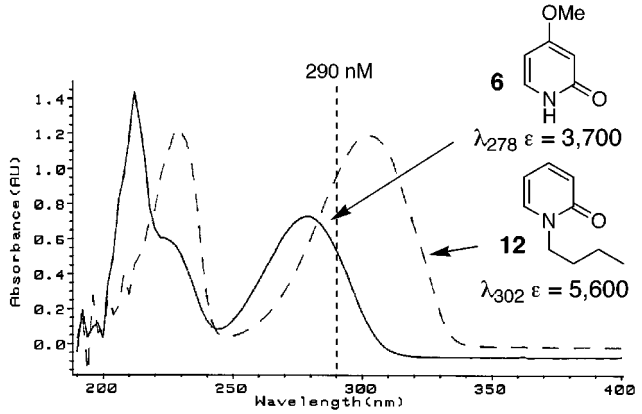


Figure 3. UV spectra of **6** and **12** in methanol.

the low conversion after 72 h and the complex mixture of products overall, did not bode well for this intermolecular reaction. Notably, however, the unreacted **6** was recovered in high yield (Table 1, entry 1).

Despite these disappointing initial results, the ability to generate a richly functionalized photoproduct **7** from simple aromatic substrates **6** and **12** was intriguing, and the high recovery of unreacted **6** suggested the possibility that the reaction outcome could be altered by changing the starting stoichiometry. Like other reactions involving two similar species where one is self-reactive,[21] increasing the relative concentration of the unreactive partner (**6**) was expected to enhance the yield of cross-product **7**. The photochemical nature of this reaction, however, requires that the appropriate chromophore be accessible. Our working assumption, that the excited state of **12** is responsible for the photochemistry, is based in part on the ability of simple 2-pyridones to undergo [4 + 4] photocycloaddition with 1,3-dienes under conditions where only the pyridones are capable of absorbing light.[22] The UV spectra of **6** and **12** are illustrated in Figure 3. Substitution of the 2-pyridone with a 4-methoxy group shifts the absorption maximum from the ca. 300 nm typical for simple pyridones, to below 280 nm, and also attenuates the extinction coefficient by one-third. The Pyrex filter used for most 2-pyridone photochemistry blocks wavelengths below 290 nm, and therefore under the reaction conditions nearly all of the light is absorbed by **12**. It is clear from the data in Figure 3 that a high relative concentration of **6** would be compatible with photoexcitation of **12**. In view of the instability of the cis isomers **8** and **14**, further experimentation with these mixtures concentrated on the isolated yields of the trans [4 + 4] products **7** and **13**, the Dewar pyridones **16** and **17**, and the percent recovery of starting 2-pyridones **6** and **12**.

The effect of altering the ratio of **6** to **12** was dramatic (Table 1). Because intermolecular photoreactions of 2-pyridones can be very concentration dependent, the overall 2-pyridone concentration was held at 0.5 M. Changing the ratio from 1:1 (entry 1) to 4:1 (entry 2) led to the complete conversion of *N*-butyl-2-pyridone **12** into photoproducts after 72 h whereas the 1:1 ratio (entry 1) led to less than 50% conversion. Further, the ratio of trans cross-product **7** to trans dimer **13** was reversed, to favor the former by a factor of 7, and the isolated yield of **7** increased from 6% to 42%. The yield of Dewar pyridone **16** remained low, and the unreacted **6** was recovered in high yield. Increasing the ratio to 7:1 continued these trends, with a 51% yield of **7** and less than 10% yield of **13**. The reaction time was found to be shorter as well, with pyridone **12** consumed within 48 h.

At the highest ratio of **6**:**12** tested, 9:1 (entry 4), the ratio of products **7** and **13** reach their highest level, with nearly 95% of the trans isomers occurring as the cross-product **7**. With a ratio of 9:1, however, some limitations become apparent. After 72 h, some *N*-butyl-2-pyridone **12** remains, and Dewar pyridone **17** appears for the first time. Both of these observations are consistent with the excess of **6** overwhelming the ability of **12** to compete for photons. For this pair of reactants, therefore, the ratio of 7:1 (entry 3) is close to ideal.

Conclusions

With this simple model system, we have found that 4-methoxy-2-pyridones (**6**) can be effectively used in [4 + 4] cycloaddition reactions with 2-pyridones lacking the 4-alkoxy substituent (**12**). The modest level of cross reactivity for **6** requires that an excess be used to limit the competing dimerization of **12**; however, the unreacted 4-methoxy-2-pyridone can be recovered in high yield and recycled. It is possible that other 2-pyridone mixtures will have optimum initial ratios other than 7:1, and further studies are in progress. The four distinct functional

(21) Classic examples include the cross-aldol reaction (Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Ed.; Pergamon: New York, 1991; Vol. 2; pp 133−179) and cross-Claisen condensation (Davis, B. R.; Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 2; pp 795−863).

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groups in cross-product **7**, alkene, enol ether, secondary amide, and tertiary amide allows for selective functionalization of this product (see following paper in this issue) and rapid synthesis of complex cyclooctanoid products from readily available materials.

Experimental Section

4-Methoxy-2-pyridone (6).[15] A solution of 4-methoxypyridine *N*-oxide **5** (2.3 g, 18 mmol) in acetic anhydride (75 mL) was heated to reflux for 6 h. The solvent was removed in vacuo, and the intermediate 2-acetoxy-4-methoxypyridine was distilled using a kugelrohr (75 °C, 0.05 mmHg). The product was dissolved in methanol/water (1:1, 20 mL) and stirred at room temperature for 1 h. The solvent was removed in vacuo, and the residue was recrystallized from acetonitrile to give **6** as colorless flakes (1.3 g, 57%). $R_f = 0.44$ (9:l methylene chloride/methanol). $\lambda_{max} = 278$ (3700). ^{1}H NMR ($CDCl_3$) δ 12.9 (br, 1H), 7.22 (d, 1H, $J = 7.2$ Hz), 5.98 (dd, 1H, $J = 2.4$, 7.3 Hz), 5.88 (d, 1H, $J = 2.4$ Hz), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 169.8, 167.4, 134.6, 101.3, 97.0, 55.4. IR (CH_2Cl_2) 1646 cm^{-1}.

***N*-Butyl-2-pyridone (12).**[17] A slurry of 2-hydroxypyridine (20 g, 0.21 mol), 1-bromobutane (45 mL, 0.4 mol), K_2CO_3 (29 g, 0.21 mol), and KI (20 mg) in methanol (200 mL) was heated to reflux for 12 h. The slurry was cooled, and the solid was removed by filtration. The filtrate was partitioned between water (100 mL) and CH_2Cl_2 (100 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried over Na_2SO_4 and concentrated to give a light brown oil. Distillation (115 °C, 0.3 mmHg) gave **12** as a colorless oil (25.4 g, 80%). $R_f = 0.38$ (3:2 ethyl acetate/hexane). $\lambda_{max} = 302$ (5,600). ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 2H), 6.46 (d, 1H, $J = 8.8$ Hz), 6.08 (t, 1H, $J = 6.7$ Hz), 3.85 (t, 2H, $J = 7.5$ Hz), 1.65 (m, 2H), 1.29 (m, 2H), 0.86 (t, 3H, 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 162.5, 139.2, 137.6, 120.9, 105.8, 49.5, 31.2, 19.8, 13.7. IR (CH_2Cl_2) 1660, 1585, 1538 cm^{-1}.

Intermolecular Photocycloaddition. A stream of dry nitrogen was passed through a solution of **6** (454 mg, 3.62 mmol) and **12** (77 mg, 0.51 mmol) in methanol (8.3 mL) in a Pyrex test tube for several minutes, and the test tube was then sealed with a septum and fitted with a nitrogen balloon. This tube was taped to the side of a water-cooled quartz cooling jacket surrounding a 450 W medium-pressure mercury lamp inside of a Pyrex filter and irradiated for a total of 72 h. The methanol was removed in vacuo, and the residue was taken up in acetonitrile. On standing, 4-methoxy-2-pyridone (**6**) crystallized from solution. The mother liquor was concentrated and chromatographed. A gradient of hexane and ethyl acetate (1:1 hexane/ethyl acetate to 100% ethyl acetate) led to the isolation of Dewar pyridone **16**, trans dimer **13**, and cis dimer **14**. Changing the solvent to 1:9 2-propanol/acetonitrile gave trans cross-product **7**, cis cross-product **8**, and residual 4-methoxy-2-pyridone (**6**).

(1α,2*β*,5*β*,6α)-3-Butyl-9-methoxy-3,7-diazatricyclo-[4.2.2.2^{2,5}]dodeca-9,11-diene-4,8-dione (7): $R_f = 0.25$ (1:9 2-propanol/acetonitrile). mp 179 °C. ^{1}H NMR ($CDCl_3$) δ 6.85 (br, 1H), 6.58 (dd, 1H, $J = 7.3$, 7.3 Hz), 6.16 (dd, 1H, $J = 7.3$, 7.3 Hz), 5.34 (dd, 1H, $J = 2.1$, 7.2 Hz), 4.18−4.12 (m, 2H), 3.85−3.74 (m, 1H), 3.60−3.51 (m, 1H), 3.51 (s, 3H), 3.38 (d, 1H, $J = 10.1$ Hz), 2.68−2.57 (m, 1H), 1.91−1.35 (m, 2H), 1.30−1.18 (m, 2H), 0.87 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$) δ 177.1, 174.7. 160.7, 133.9, 133.1, 98.0, 55.9, 55.8, 55.7, 52.8, 48.1, 45.3, 30.0, 19.9, 13.8. IR (CH_2Cl_2) 3420, 1688, 1658 cm^{-1}. Exact mass (FAB) *m*/*z* calcd for $C_{15}H_{21}N_20_3$: 277.1552, found: 277.1553. Anal. Calcd for $C_{15}H_{20}N_20_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.11; H, 7.29; N, 10.09.

(1α,2α,5α,6α)-3-Butyl-9-methoxy-3,7-diazatricyclo-[4.2.2.2^{2,5}]dodeca-9,11-diene-4,8-dione (8): $R_f = 0.4$ (1:9 2-propanol/acetonitrile). ^{1}H NMR ($CDCl_3$) δ 6.85 (d, 1H), 6.28−6.18 (m, 2H), 4.96 (dd, 1H, $J = 7.2$, 2 Hz), 4.29−4.16 (m, 2H), 3.93−3.81 (m, 1H), 3.69−3.52 (m, 1H), 3.52 (s, 3H), 3.34 (d, 1H, $J = 10$ Hz), 2.90−2.79 (m, 1H), 1.89−1.18 (m, 4H), 0.87 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$) δ 174.6, 173.8, 163.5, 134.4, 130.0, 95.4, 56.9, 55.7, 55.3, 52.7, 48.4, 45.7, 29.3, 19.9, 13.8.

(1α,2*β*,5*β*,6α)-3,7-Dibutyl-3,7-diazatricyclo[4.2.2.2^{2,5}]-dodeca-9,11-diene-4,8-dione (13):[9] $R_f = 0.17$ (1:1 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 6.60 (dd, 2H, $d = 1.6$, 6.8 Hz), 6.15 (dd, 2H, $J = 1.2$, 8.2 Hz). 4.08−4.01 (m, 2H), 3.83−3.71 (m, 2H), 3.60−3.52 (m, 2H), 2.49−2.38 (m, 2H), 1.57−1.37 (m, 4H), 1.32−1.17 (m, 4H), 0.89 (t, 6H, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$) δ 174.2, 134.9, 130.4, 56.0, 50.7, 47.1, 29.6, 20.0, 13.7. IR (CH_2Cl_2) 1649 cm^{-1}.

(1α,2α,5α,6α)-3,7-Dibutyl-3,7-diazatricyclo[4.2.2.2^{2,5}]-dodeca-9,11-diene-4,8-dione (14):[9] $R_f = 0.3$ (1:1 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 6.24−6.16 (m, 4H), 4.23−4.16 (m, 2H), 3.90−3.79 (m, 2H), 3.65−3.57 (m. 2H); 2.94−2.82 (m, 2H), 1.50−1.35 (m, 4H), 1.34−1.15 (m, 4H). 0.87 (t, 6H, $J = 7.3$ Hz). ^{13}C NMR ($CDCl_3$) δ 173.0, 133.9, 132.0, 58.1, 52.4, 49.6, 45.9, 29.5, 19.9, 13.8.

4b,7,8a,8b-Tetrahydro-1,7-dibutyl-(4aα,4bα,8aα,8bα)-cyclobuta[1,2-*b*:4,3-*c*′]dipyridine-2,8-(1*H*,4a*H*)-dione (15):[9] $R_f = 0.43$ (1:1 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 6.41 (d, 1H, $J = 10.0$ Hz), 6.01 (d, 1H, $J = 8.0$ Hz), 5.80 (d, 1H, $J = 9.7$ Hz), 4.76 (dd, 1H, $J = 5.7$, 8.0 Hz), 4.50 (t, 1H, $J = 8.7$ Hz), 3.98 (m, 1H), 3.62−3.40 (m, 3H), 3.35 (m, 1H), 3.13 (pentet, 1H, $J = 7.1$ Hz), 2.85 (pentet, 1H, $J = 7.1$ Hz), 1.7−1.2 (m, 8H), 1.05−0.80 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 165.4, 162.6, 137.3, 131.5, 125.6, 99.7, 54.6, 46.9, 45.0, 44.3, 41.9, 34.6, 30.0, 29.5, 20.2, 20.0, 13.9, 13.6.

2-Butyl-2-azabicyclo[2.2.0]hex-5-en-3-one (16):[9] $R_f = 0.70$ (3:2 hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 6.55 (m, 2H), 4.30 (s, 1H), 4.10 (s, 1H), 3.20 (m, 1H), 3.05 (m, 1H), 1.45 (m, 2H), 1.35 (m, 2H), 0.90 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$) δ 170.0, 141.1, 140.4, 57.5, 54.0, 43.0, 29.5, 20.1, 13.7. IR (neat) 1737, 1505 cm^{-1}.

5-Methoxy-2-azabicyclo[2.2.0]hex-5-en-3-one (17):[16] ^{1}H NMR ($CDCl_3$) δ 6.07 (br, 1H), 5.05 (s, 1H), 4.25 (m, 2H), 3.67 (s, 3H).

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Supporting Information Available: ^{1}H NMR spectra for **6**−**8**, **12**−**17**, COSY spectra for **7**, **8**, **13**, **14**, and HETCOR spectra for **13** (14 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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