3-Hydroxy-4-pyrones as Precursors of 4-Methoxy-3-oxidopyridinium Ylides. An Expeditious Entry to Highly Substituted 8-Azabicyclo[3.2.1]octanes

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Received May 8, 1996[⊗]

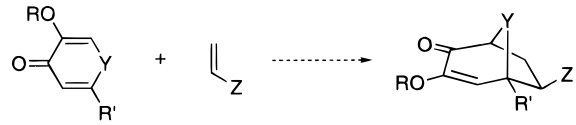
3-Hydroxy-4-pyridones, which are easily prepared from commercially available 3-hydroxy-4-pyrones, can be readily transformed into 4-methoxy-3-oxidopyridinium ylides by treatment with methyl trifluoromethanesulfonate and subsequent deprotonation with a non-nucleophilic base. These ylides are capable of undergoing cycloaddition to several electron-deficient alkenes, thus allowing the synthesis of highly functionalized azabicyclo[3.2.1]octane moieties. The rich substitution patterns of these frameworks might allow their divergent conversion to a variety of natural and non-natural tropane alkaloids.

Introduction

Whereas the Diels−Alder reaction has been of major utility in the synthesis of both carbo- and heterocyclic six-membered rings, cycloaddition reactions that form seven-membered rings have been much less common.[2] Recently, we reported a new, practical, stereoselective route to highly functionalized [3.2.1] oxabicyclic systems (**2a**, Scheme 1) based on the *thermal* [5 + 2] cycloaddition of 3-alkoxy-4-pyrones to temporarily connected alkenes.[3] The simplicity of the process and the ready availability of the starting pyrones, coupled to the rich but differentiated functionalization of the cycloadducts, augurs interesting synthetic applications of this methodology.[4]

On the basis of these precedents, and bearing in mind the presumable rapid accessibility of 3-alkoxy-4-pyridones (**1b**) from the corresponding pyrones,[5] we decided to investigate the feasibility of using the former as "off-the-shelf" five-carbon cycloaddition precursors of highly functionalized 8-azabicyclo[3.2.1]octane skeletons (**2b**). This was of interest because this bicyclic system is the characteristic structural element of the tropane alkaloids, an important family of bioactive natural products.[6] Although a large number of interesting methods for the synthesis of tropane alkaloids have already been developed,[7] they are mostly inappropriate for the rapid assembly of highly substituted analogs. We hoped that the above approach might supplement the current strategies by providing a novel and expeditious entry to a variety of highly functionalized tropane derivatives.

Scheme 1



1a, Y = O
1b, Y = NR''

2a, Y = O
2b, Y = NR''

Results and Discussion

In order to test the feasibility of the approach, pyridone **7** was synthesized from commercially available kojic acid (**3**) following the steps shown in Scheme 2. Reaction of the chloropyrone **4** with allylmercaptan and triethy-

⊗ Abstract published in *Advance ACS Abstracts,* August 1, 1996.

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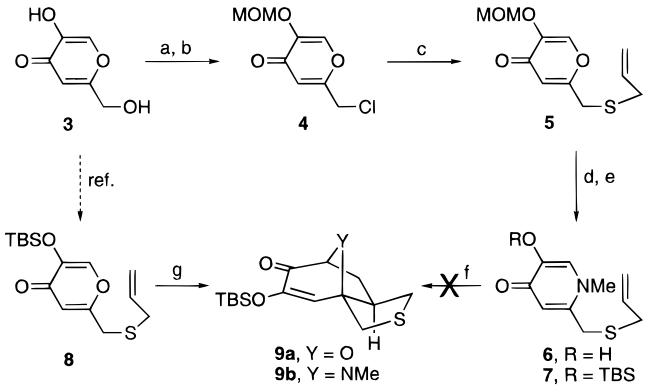
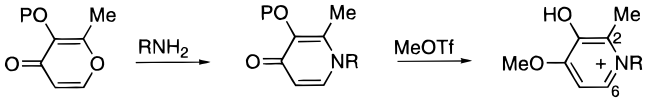
S0022-3263(96)00854-7 CCC: $12.00

Scheme 2[a]



[a] Key: (a) MOMCl, DIEA; (b) $SOCl_2$; (c) $CH_2{=}CHCH_2SH$, Et_3N; (d) (i) $MeNH_2$, (ii) HCl; (e) TBSCl, imidazole; (f) toluene, 140−190 °C; (g) toluene, 140 °C.

Scheme 3



lamine gave the allyl thioether **5**, which was transformed into the pyridone **6** by reaction with methylamine followed by acidic workup (58% overall yield). Treatment of **6** with TBSCl and imidazole provided the pyridone **7** in quantitative yield. Unfortunately, unlike the homologous pyrone (**8**), which gives the corresponding cycloadduct **9a** by thermolysis at 140 °C,[3] pyridone **7** remained unchanged after heating in toluene for several hours, even at 190 °C. Although the mechanism of the thermal [5C + 2C] pyrone−alkene cycloaddition is unclear, the fact that the pyridone is much less reactive than the pyrone is presumably associated with the greater aromatic character of the former.[8]

Since it is known that simple 3-oxidopyridinium ylides undergo dipolar cycloaddition reactions with a variety of activated alkenes,[7j,9] we reasoned that transformation of the 3-alkoxy-4-pyridones into 4-methoxy-3-oxidopyridinium ylides might provide a way to accomplish the [5C + 2C] cycloaddition.[10] The feasibility of this strategy was initially investigated for intermolecular cases.

Reaction of 3-(benzyloxy)maltol (**10b**) with $MeNH_2$ afforded the pyridone **11b** (Scheme 3), which was readily converted to the 3-hydroxy-4-pyridone **11a** by hydrogenation (78% yield for the two steps).[5a] The latter compound can also be prepared directly from maltol (**10a**), although in much lower yield (16%).[5c] Heating of a solution of **11a** in $CHCl_3$ with 1.5 equiv of MeOTf provided the pyridinium salt **12**.[11]

Initial attempts to induce the dipolar cycloaddition of **12** were conducted using DBU as ylide-generating base

Table 1. Cycloaddition of Pyridinium Salts 12 and 13 to Several Dipolarophiles

salt	dipolarophile	products (*exo*:*endo*)	combined yield (%)
12	*N*-phenylmaleimide	**14**	72
12	acrylonitrile	**16/20** (56:44)	68
12	methyl acrylate	**17/21** (58:42)	64
12	phenyl vinyl sulfone	**18/22** (80:20)	58
13	*N*-phenylmaleimide	**15**	78
13	acrylonitrile	**19/23** (55:45)	69

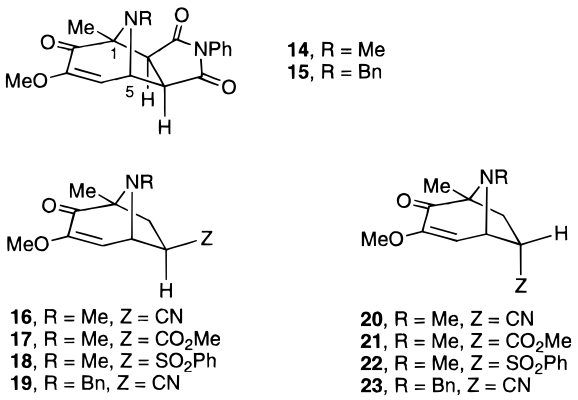


Figure 1.

and *N*-phenylmaleimide as activated dipolarophile. Under these conditions the dipolarophile was rapidly consumed, but no cycloadducts were detected in the reaction mixture. We assumed that the disappearance of the dipolarophile was due to a base-induced side reaction and tried the weaker base 2,2,6,6-tetramethylpiperidine (TMP). Satisfyingly, stirring a mixture of the crude pyridinium salt **12** and *N*-phenylmaleimide (5 equiv) in refluxing CH_3CN in the presence of 1.5 equiv of TMP for 6 h gave the *exo* adduct **14** smoothly in over 72% isolated yield. The stereochemistry of the adduct was deduced from the negligibly small coupling constant across the 5,6 positions.

The cycloaddition reaction also succeeded with several asymmetric electron-deficient alkenes, such as acrylonitrile, methyl acrylate, and phenyl vinyl sulfone, but in these cases mixtures of *exo* and *endo* stereoisomers were obtained (Table 1, Figure 1). The regio- and stereochemical assignments follow from the chemical shifts and coupling patterns observed in their ^1H NMR spectra. The reaction with phenyl vinyl sulfone is particularly promising because reductive removal of the sulfone group at some suitable stage in the azabicycle elaboration would afford the typical 6,7 unsubstituted tropane system.[12]

The complete regioselectivity of the reaction can be easily rationalized on the basis of the frontier molecular orbital theory.[13] Semiempirical calculations predict that the HOMO of the 4-methoxy-3-oxidopyridinium ylide has a larger coefficient for position 2 (−0.58) than for position 6 (+0.47).[14] Since for electron-deficient alkenes the Cβ coefficient of the LUMO is larger than the Cα, the dominant interaction between the frontier orbitals ac-

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(10) This type of transformation has previously been used to convert the homologous pyrones into pyrilium salts: see ref 2j,k.

(11) This salt can be crystallized from EtOAc or used directly as a crude reagent in the cycloaddition step.

(12) The reductive removal of the sulfone group has previously been described for related bicyclic systems: Pandey, G.; Lakshamaiah, G.; Ghatak, A. *Tetrahedron Lett.* **1993**, *34*, 7301.

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(14) Approximate frontier orbital coefficients at the reaction centers of these pyridinium betaines were calculated by the PM3 method using the MOPAC program.

counts for the experimental result. Furthermore, comparison of the coefficients at the reactive centers of the HOMO of our betaine with those of the parent unsubstituted 3-oxidopyridinium dipole reveals that the presence of the 4-methoxy group induces a slight but significant increase in their size difference.[15] These data may explain the entire regioselectivity of our reactions in comparison with that reported for cycloadditions with 4-unsubstituted oxidopyridinium ylides.[13]

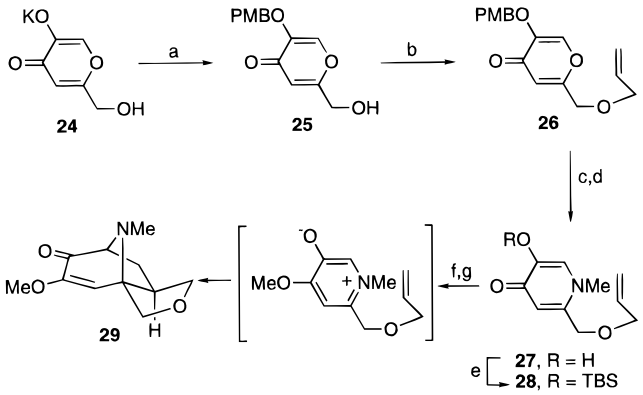
We also evaluated the possibility of using primary amines other than methylamine to convert the pyrones into pyridones and, hence, of preparing azabicycles with different substituents at the nitrogen. This was of interest not only as an entry to novel tropanes with modulated biological properties[6d] but also as a potential way to introduce asymmetry in the system.[16] Reaction of the 3-(methoxymethyl)maltol derivative **10c** with $BnNH_2$, followed by acidic deprotection, afforded the 3-hydroxy-4-pyridone **11c** in 70% yield. Treatment of this pyridone with MeOTf provided the crude pyridinium salt **13**, which was used directly in cycloaddition reactions with *N*-phenylmaleimide and acrylonitrile. The selectivity and efficiency of these reactions were similar to those obtained with the *N*-methyl analog (Table 1).

Having demonstrated the validity of the methodology for rapid bimolecular assembly of richly substituted 8-azabicyclo[3.2.1]octenones, we turned our attention to the intramolecular processes, which would allow the stereoselective synthesis of an unprecedented type of fused tropanes.[17] The preparation of this type of tropanes by alternative methods is hampered by the requirement of running a multistage synthesis for setting up the appropriate precursors.[18]

Initial attempts to prepare the pyridinium salt of pyridone **6** by selective O-4 methylation were thwarted by the presence of the side chain sulfur atom. We therefore prepared a cycloaddition precursor bearing an ether rather than a thioether tether (Scheme 4). Treatment of the (*p*-methoxybenzyl)kojic acid derivative **25** with allyl bromide and KO-*t*-Bu produced the ether **26** although in very low yield (15%). However, when the reaction was carried out with KF adsorbed on alumina,[19] the desired ether was obtained in a 92% yield. Reaction of **26** with methylamine and removal of the protecting group in an acidic medium gave the expected 3-hydroxy-4-pyridone **27** in 81% yield.

As in the case of pyridone **7**, thermolysis of the silylated derivative **28** in toluene for several hours at 140−190 °C failed to give any cycloadduct (mainly affording starting material), but reflux of a solution of **27** in $CHCl_3$ with MeOTf, removal of the solvents in vacuo, and treatment of an acetonitrile solution of the resulting crude with TMP in a sealed tube at 100 °C provided the desired *exo* cycloadduct **29** in 95% yield. Overall, a readily available pyrone (kojic acid) was transformed in only a few steps into a tricyclic adduct with a much higher degree of structural, stereochemical, and functional complexity.[20]

Scheme 4[a]



[a] Key: (a) PMBCl, Bu_4NI; (b) $CH_2{=}CHCH_2Br$, KF, alumina; (c) $MeNH_2$; (d) TFA; (e) TBSCl, imid; (f) MeOTf; (g) TMP, CH_3CN, reflux.

Conclusion

In contrast to their parent pyrones, 3-alkoxy-4-pyridones fail to undergo direct thermal [5C + 2C] cycloaddition to alkenes. The annulation can, however, be achieved driving the reaction through a dipolar mechanism, by converting the pyridones into 4-methoxy-3-oxidopyridinium ylides. The rich substitution pattern of the resulting 8-azabicyclo[3.2.1]octane adducts might allow their divergent conversion to a variety of novel tropane derivatives. Thus, although 3-hydroxy-4-pyrones have no obvious structural resemblance to the tropane azabicyclic skeleton, viewing the former as oxidopyridinium ylide precursors led to a new, practical entry to the second. Our current work in this area is focused on the divergent manipulation of the cycloadducts to obtain tropane analogs of potential biological interest and on the development of asymmetric versions of the cycloaddition.

Experimental Section

General Procedures. All reactions were conducted in dry solvents under argon atmosphere unless otherwise stated. The dry solvents were freshly distilled under argon from the appropriate drying agent, before use: toluene and THF from sodium/benzophenone; CH_2Cl_2, $CHCl_3$, and CCl_4 from P_2O_5, and CH_3CN and Et_3N from CaH_2. DMF was distilled from P_2O_5 under vacuum and stored in the presence of type 4A molecular sieves. Thin layer chromatography (TLC) was performed on silica gel plates, and components were visualized by observation under UV light or by heating the plates after treatment with a phosphomolybdic reagent. Dryings were performed with anhydrous Na_2SO_4. Melting points (open capillary tubes) are uncorrected.

^1H and ^{13}C NMR spectra were recorded at 250 and 62.83 MHz, respectively, in $CDCl_3$, unless otherwise indicated. Chemical shifts are reported in ppm (δ). Assignment of the ^1H NMR signals of some compounds was based on decoupling and COSY experiments. Carbon types were determined from DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were measured at 70 eV, and relative intensities are given in parentheses.

(15) Calculations performed with the same method show a coefficient of −0.53 (C_2) and 0.50 (C_6) in the HOMO of the 4-unsubstituted pyridinium salt.

(16) Previous attempts to induce asymmetry in simple oxidopyridinium cycloadditions have been based on the introduction of the chiral auxiliary in the dipolarophile, which leads to poor stereofacial selectivity: Takahashi, T; Fujii, A.; Sugita, J.; Hagi, T.; Kitano, K.; Arai, Y.; Koizume, T. *Tetrahedron Asymmetry* **1991**, *2*, 1379.

(17) There is a current interest in the preparation of related fused tropanes: Davies, H. M. L.; Matasi, J. J.; Ahmed, G. *J. Org. Chem.* **1996**, *61*, 2305.

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2-(Chloromethylene)-5-[(methoxymethylene)oxy]-4-pyrone (4). Diisopropylethylamine (8.2 mL, 46.7 mmol) and methoxymethylene chloride (3.51 mL, 46.7 mmol) were added to a solution of 2-(chloromethylene)-5-hydroxy-4-pyrone[3] (5 g, 31.1 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred for 3 h at room temperature. The reaction mixture was poured into brine and extracted with CH_2Cl_2. The combined organic layers were dried and concentrated. The residue was chromatographed (30−70% EtOAc/hexanes) to give 6.24 g of the pyrone **4** [99%, R_f 0.24 (EtOAc), white solid, mp 63−65 °C]: ^{1}H NMR δ 7.89 (1H, s), 6.44 (1H, s), 5.08 (2H, s), 4.29 (2H, s), 3.44 (3H, s); ^{13}C NMR δ 174.1 (C), 161.7 (C), 146.2 (C), 143.0 (CH), 115.2 (CH), 95.8 (CH_2), 56.4 (CH_3), 40.8 (CH_2); LRMS *m/z* 204 (M^+, 4), 203 (14), 191 (13), 189 (38), 175 (15), 173 (42), 169 (17), 161 (13), 146 (36), 145 (23), 144 (100), 138 (19), 95 (37), 69 (10), 67 (11), 58 (25); HRMS calcd for $C_8H_9O_4Cl$ 204.018 94, found 204.018 70.

2-[(Allylthio)methylene]-5-[(methoxymethylene)oxy]-4-pyrone (5). Triethylamine (5.0 mL, 39.1 mmol) and allylmercaptane (3.2 mL, 39.1 mmol) were added to a solution of **4** (4 g, 19.5 mmol) in THF (50 mL). The mixture was stirred for 3 days at room temperature, poured into a saturated solution of $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was dried and concentrated. The residue was purified by flash chromatography (30−70% EtOAc/hexanes) to give 3.92 g of the pyrone **5** [83%, R_f 0.51 (50% EtOAc/hexanes), white solid, mp 48−50 °C]: ^{1}H NMR δ 7.86 (1H, s), 6.30 (1H, s), 5.71 (1H, m), 5.11 (2H, m), 5.09 (2H, s), 3.46 (3H, s), 3.40 (2H, s), 3.12 (2H, d, J = 6.1 Hz); ^{13}C NMR δ 174.1 (C), 164.5 (C), 145.5 (C), 143.1 (CH_2), 132.9 (CH_2), 118.3 (CH), 114.2 (CH_2), 95.2 (CH), 56.1 (CH_3), 34.2 (CH_2), 31.3 (CH_2); LRMS *m/z* 242 (M^+, 13), 227 (63), 185 (20), 182 (100), 168 (48), 156 (34), 140 (13), 110 (25), 95 (41), 87 (16), 73 9 (11), 69 (24), 53 (16); HRMS calcd for $C_{11}H_{14}O_4S$ 242.061 228, found 242.061 49.

2-[(Allylthio)methylene]-5-hydroxy-1-methyl-4-pyridone (6). Aqueous methylamine (40%, 7 mL, 90 mmol) was added a solution of **5** (3 g, 12.4 mmol) in ethanol (15 mL). The mixture was stirred overnight at room temperature. The solvent was evaporated and the resulting residue partitioned between water and CH_2Cl_2. The aqueous phases were further extracted with CH_2Cl_2 and the combined organic extracts dried and concentrated. Although the residue (3.2 g) was directly subjected to the deprotection step, a small amount was purified by flash chromatography (0−10% MeOH/CH_2Cl_2) in order to complete its characterization. The expected product, **2-[(allylthio)methylene]-5-[(methoxymethylen)oxy]-1-methyl-4-pyridone**, was obtained as a red solid [R_f 0.64 (10% MeOH/CH_2Cl_2), mp 71−73 °C]: ^{1}H NMR δ 7.22 (1H, s), 6.14 (1H, s), 5.60 (1H, m), 5.08 (2H, m), 5.02 (2H, s), 3.58 (3H, s), 3.35 (5H, s), 3.0 (2H, d, J = 6.9 Hz); ^{13}C NMR δ 172.5 (C), 146.6 (C), 144.6 (C), 133.1 (CH), 130.1 (CH), 118.6 (CH_2), 118.6 (CH), 95.6 (CH_2), 56.3 (CH_3), 40.6 (CH_3), 33.5 (CH_2), 31.1 (CH_2); LRMS *m/z* 255 (M^+, 10), 254 (44), 241 (14), 240 (100), 212 (11), 198 (13), 195 (52), 182 (29), 170 (69), 153 (41), 150 (20), 139 (38), 124 (21), 110 (32); HRMS calcd for $C_{12}H_{17}O_3NS$ 255.092 92, found 255.092 56.

A solution of 2 g of the residue obtained from the previous experiment in THF/H_2O (10:1, 22 mL) was stirred with HCl (10%, 1 mL) for 20 h at room temperature. The mixture was carefully poured into a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (50 × 3) The combined organic layers were dried and concentrated. The residue was subjected to flash cromatography (0−10% MeOH/CH_2Cl_2) to give 1.23 g of the pyridone **6** [72% from **5**, R_f 0.50 (10% MeOH/CH_2Cl_2), red solid, mp 98−100 °C]: ^{1}H NMR [$(CD_3)_2SO$] δ 7.45 (1H, s), 6.14 (1H, s), 5.77 (1H, m), 5.18 (2H, m), 3.65 (5H, broad s), 3.15 (2H, d, J = 6 Hz); ^{13}C NMR [$(CD_3)_2SO$] δ 170.4 (C), 147.3 (C), 143.9 (C), 134.1 (CH), 125.2 (CH), 117.8 (CH_2), 114.4 (CH), 39.5 (CH_3), 33.4 (CH_2), 31.0 (CH_2); LRMS *m/z* 211 (M^+, 19), 139 (25), 138 (77), 111 (10), 110 (100), 71 (8), 67 (11), 58 (25); HRMS calcd for $C_{10}H_{13}O_2NS$ 211.066 70, found 211.066 74. Anal. Calcd for $C_{10}H_{13}O_2NS$: C, 56.849; H, 6.202; N, 6.630. Found: C, 56.76; H, 6.75; N, 6.57.

2-[(Allylthio)methylene]-5-[(*tert*-butyldimethylsilyl)oxy]-1-methyl-4-pyridone (7). Triethylamine (0.1 mL, 1.4 mmol), *tert*-butyldimethylsilyl chloride (225 mg, 1.4 mmol), and a catalytic amount of DMAP were added to a solution of **6** (200 mg, 0.9 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 30 min, poured into brine, and extracted with CH_2Cl_2. The organic layers were dried, filtered, and concentrated. The residue was chromatographed on neutral alumina (deactivated with 6% H_2O) to afford 280 mg of **7** [91%, R_f 0.78 (EtOAc), viscous oil]: ^{1}H NMR δ 7.18 (1H, s), 6.14 (1H, s), 5.66 (1H, m), 5.11 (2H, m), 3.63 (3H, s), 3.59 (2H, s), 3.19 (2H, d, J = 6.4 Hz), 0.92 (9H, s), 0.18 (6H, s).

3-(Benzyloxy)-2-methyl-4-pyrone (10b). Potassium hydroxide (5.4 g, 95.1 mmol) was added to a solution of 3-hydroxy-2-methyl-4-pyrone (8 g, 63.4 mol) in dry MeOH (150 mL). When the mixture was homogeneous, benzyl bromide (11.6 mL, 95.1 mmol) was added. The reaction mixture was stirred overnight at room temperature. After evaporation of the solvent, the crude was poured into brine and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried, filtered, and concentrated. The residue was purified by flash chromatography (25−75% EtOAc/hexanes) to give 13.55 g of the pyrone **10b** [99%, R_f 0.53 (Et_2O), viscous oil]: ^{1}H NMR δ 7.55 (1H, d, J = 5.7 Hz), 7.33 (5H, m), 6.30 (1H, d, J = 5.7 Hz), 5.11 (2H, s), 2.04 (3H, s); ^{13}C NMR δ 175.1 (C), 159.7 (C), 153.6 (CH), 143.8 (C), 136.9 (C), 129.0 (CH), 128.4 (CH), 128.3 (CH), 117.1 (CH), 73.5 (CH_2), 14.6 (CH_3); LRMS *m/z* 217 (M^+, 3.8), 216 (25), 110 (14), 91 (100), 69 (5), 65 (13); HRMS calcd for $C_{13}H_{12}O_3$ 216.078 64, found 216.079 00. Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.210; H, 5.593. Found: C, 72.19; H, 5.52.

3-(Benzyloxy)-1,2-dimethyl-4-pyridone (11b). Aqueous methylamine (40%, 50 mL, 650 mmol) was added to a solution of **10b** (12 g, 55.2 mmol) in absolute EtOH (140 mL). The mixture was stirred for 22 h at room temperature. The solvent was evaporated, and the crude was poured into water and extracted with CH_2Cl_2 (4 × 200 mL). The organic extracts were dried, filtered, and concentrated. The residue was purified by flash chromatography (2−10% MeOH/CH_2Cl_2) to give 12.53 g of the pyridone **11b** [99%, R_f 0.55 (10% MeOH/CH_2Cl_2), viscous oil]: ^{1}H NMR δ 7.27 (5H, m), 7.11 (1H, d, J = 7.4 Hz), 6.23 (1H, d, J = 7.5 Hz), 5.10 (2H, s), 3.4 (3H, s), 2.00 (3H, s); ^{13}C NMR δ 173.3 (C), 146.3 (C), 141.2 (C), 139.1 (CH), 137.7 (C), 128.9 (CH), 128.3 (CH), 127.9 (CH), 116.9 (CH), 72.8 (CH_2), 41.3 (CH_3), 12.7 (CH_3); LRMS *m/z* 230 (M^+, 8), 229 (51), 228 (8), 152 (12), 149 (5), 138 (32), 124 (14) 123 (100), 122 (14), 110 (62), 91 (52); HRMS calcd for $C_{14}H_{15}O_2N$ 229.110 28, found 229.110 44.

1,2-Dimethyl-3-hydroxy-4-pyridone (11a). Palladium on activated carbon (1.2 g, 5%) was added to a solution of **11b** (12 g, 52.2 mmol) in MeOH (150 mL), and the mixture was stirred under H_2 for 2 h. The suspension was filtered through celite and washed with hot MeOH. The solvent was evaporated and the residue chromatographed to give 5.83 g of **11a** [80%, R_f 0.47 (10% MeOH/CH_2Cl_2), white solid]. The pure compound was crystallized from MeOH: mp 272−276 °C; ^{1}H NMR δ: 7.22 (1H, d, J = 7.4 Hz), 6.37 (1H, d, J = 7.3 Hz), 3.65 (3H, s), 2.39 (3H, s); ^{13}C NMR δ 169.7, 146.3, 137.5, 128.3, 110.9, 41.5, 12.1; LRMS *m/z* 139 (M^+, 100), 123 (9), 111(16), 110 (66), 105 (20), 97 (10), 91 (26); HRMS calcd for $C_7H_9O_2N$ 139.063 33, found 139.063 45. Anal. Calcd for $C_7H_9O_2N$: C, 60.420; H, 6.51; N, 10.006. Found: C, 60.62; H, 6.63; N, 10.10.

1,2-Dimethyl-3-hydroxy-4-methoxypyridinium Trifluoromethanesulfonate (12). Freshly distilled methyl trifluoromethanesulfonate (1.39 g, 8.5 mmol, 960 mL) was added to a solution of **11a** (1.0 g, 7.1 mmol) in $CHCl_3$ (50 mL). The mixture was refluxed for 3 h and the solvent evaporated under vacuum. The solid residue was crystallized from EtOAc to give 1.94 g of the salt **12** [90%, white solid, mp 105−107 °C]: ^{1}H NMR [$(CD_3)_2CO$] δ 9.81 (1H, br s), 8.52 (1H, d, J = 7.1 Hz), 7.55 (1H, d, J = 7.1 Hz), 4.28 (3H, s), 4.18 (3H, s), 2.71 (3H, s); ^{13}C NMR [$(CD_3)_2CO$] δ 159.7 (C), 144.7 (C), 143.3 (C), 140.7 (CH), 108.3 (CH), 58.3 (CH_3), 45.4 (CH_3), 13.1 (CH_3). Anal. Calcd for $C_9H_{12}O_5SNF_3$: C, 35.46; H, 3.83; N, 4.59. Found: C, 35.65; H, 3.99; N, 4.62.

(1*R,5*R**,6*S**,7*S**)-1,8 Dimethyl-3-methoxy-2-oxo-*N*-phenyl-8-azabicyclo[3.2.1]oct-3-ene-6,7-*exo*-dicarboximide (14).** 2,2,6,6-Tetramethylpiperidine (0.16 mL, 0.99 mmol) was added to a solution of **12** (200 mg, 0.66 mmol) and *N*-phenylmalemide (570 mg, 3.3 mmol) in CH_3CN (10 mL). The

mixture was refluxed for 2 h, poured into water, and extracted with CH_2Cl_2. The organic layer was dried and concentrated and the residue purified by flash chromatography (20−50% EtOAc/hexanes) to give 154 mg of the cycloadduct **14** [72%, R_f 0.72 (EtOAc), white solid, mp 151−153 °C]: ^{1}H NMR δ 7.36 (5H, m), 5.83 (1H, d, J = 5.5 Hz), 4.30 (1H, d, J = 5.5Hz), 3.63 (3H, s), 3.37 (1H, d, J = 7.4 Hz), 3.02 (1H, d, J = 7.4 Hz), 2.32 (3H, s), 1.39 (3H, s); ^{13}C NMR δ 193.7 (C), 175.8 (C), 173.6 (C), 150.6 (C), 131.9 (C), 129.2 (CH), 128.8 (CH), 126.4 (CH), 111.2 (CH), 72.3 (C), 61.7 (CH), 55.1 (CH_3), 51.8 (CH), 48.5 (CH), 31.5 (CH_3), 15.8 (CH_3); LRMS m/z 326 (M^+, 3), 284 (19), 283 (100), 173 (61), 153 (22), 136 (43), 125 (84), 122 (18), 119 (18), 108 (29), 94 (31), 91 (24), 77 (18), 64 (18), 56 (57), 54 (23), 53 (23); HRMS calcd for $C_{18}H_{18}O_4N_2$ 326.126 66, found 326.127 12. Anal. Calcd for $C_{18}H_{18}O_4N_2$: C, 66.247; H, 5.559; N, 8.584. Found: C, 65.89; H, 5.75; N, 8.32.

(1*R,5*R**,6*S**)-6-*exo*-Cyano-1,8 dimethyl-3-methoxy-8-azabicyclo[3.2.1]oct-3-en-2-one (16) and (1*R**,5*R**,6*R**)-6-*endo*-Cyano-1,8-dimethyl-3-methoxy-8-azabicyclo[3.2.1]-oct-3-en-2-one (20).** Acrylonitrile (15 mL, 24.6 mmol) was added to a solution of the oxidopyridinium salt **12** (800 mg, 2.6 mmol) in CH_3CN (20 mL). 2,2,6,6-Tetramethylpiperidine (0.64 mL, 4 mmol) was slowly added, and the mixture was heated under reflux for 10 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was dried and concentrated and the residue purified by flash chromatography (25−50% EtOAc/hexanes) to afford **16** (205 mg) and **20** (164 mg) as white solids (68% overall yield). **16** [R_f 0.40 (EtOAc), cryst. Et_2O mp 139−141 °C]: ^{1}H NMR δ 5.62 (1H, d, J = 5.6 Hz), 4.32 (1H, d, J = 5.6 Hz), 3.59 (3H, s), 2.87 (1H, t, J = 6.4 Hz), 2.36 (3H, s), 2.24 (2H, d, J = 6.4 Hz), 1.36 (3H, s); ^{13}C NMR δ 195.4 (C), 151.1 (C), 121.8 (C), 109.1 (CH), 69.8 (C), 64.2 (CH), 55.1 (CH_3), 37.6 (CH_2), 31.9 (CH), 31.4 (CH_3), 17.7 (CH_3); LRMS m/z 206 (M^+, 5), 178 (43), 163 (100), 152 (12), 148 (20), 147 (30), 135 (25), 125 (26), 106 (23), 94 (19), 56 (56); HRMS calcd for $C_{11}H_{14}O_2N_2$ 206.105 53, found 206.105 55. Anal. Calcd for $C_{11}H_{14}O_2N_2$: C, 64.061; H, 6.842; N, 13.583. Found: C, 64.126; H, 6.92; N, 13.56. **20** [R_f 0.59 (EtOAc), cryst CH_2Cl_2/Et_2O (1:1) mp 150−152 °C]: ^{1}H NMR δ 5.68 (1H, d, J = 5.5 Hz), 4.01 (1H, t, J = 5.5 Hz), 3.57 (3H, s), 3.28 (1H, ddd, J = 5.5, 6.2, 10.3 Hz), 2.27 (1H, dd, J = 10.3, 13.9 Hz), 2.19 (3H, s), 1.93 (1H, dd, J = 6.3, 13.9 Hz), 1.19 (3H, s); ^{13}C NMR δ 195.1 (C), 151.1 (C), 120.0 (C), 108.9 (CH), 70.1 (C), 61.8 (CH), 55.2 (CH_3), 37.1 (CH_2), 32.2 (CH), 30.6 (CH_3), 17.4 (CH_3); LRMS m/z 206 (M^+, 8), 178 (22), 163 (52), 148 (11), 147 (18), 125 (16), 106 (16), 69 (13), 57 (22), 56 (100). Anal. Calcd for $C_{11}H_{14}O_2N_2$: C, 64.061; H, 6.842; N, 13.583. Found: C, 63.93; H, 6.95; N, 13.58.

(1*R,5*R**,6*S**)-1,8-Dimethyl-3-methoxy-6-*exo*-(methoxycarbonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (17) and (1*R**,5*R**,6*R**)-1,8-Dimethyl-3-methoxy-6-*endo*-(methoxycarbonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (21).** Methyl acrylate (15 mL, 24.6 mmol) was added to a solution of **12** (800 mg, 2.6 mmol) in CH_3CN (20 mL). 2,2,6,6-Tetramethylpiperidine (0.64 mL, 4 mmol) was slowly added and the mixture heated under reflux for 10 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was dried and concentrated and the residue purified by flash chromatography (25−75% EtOAc/hexanes) to afford the compounds **17** (261 mg) and **21** (142 mg) as white solids, with a total yield of 64%. **17** [R_f 0.27 (EtOAc), cryst. Et_2O mp 101−102 °C]: ^{1}H NMR δ 5.69 (1H, d, J = 5.6 Hz), 4.15 (1H, d, J = 5.6 Hz), 3.69 (3H, s), 3.56 (3H, s), 2.79 (1H, dd, J = 3.4, 9.5 Hz), 2.40 (1H, dd, J = 3.4, 14.0 Hz), 2.25 (3H, s), 1.97 (1H, dd, J = 9.5, 14.0 Hz), 1.26 (3H, s); ^{13}C NMR δ 196.7 (C), 173.4 (C), 150.6 (C), 111.3 (CH), 70.1 (C), 63.2 (CH), 54.8 (CH_3), 52.2 (CH_3), 46.9 (CH), 35.2 (CH_2), 31.9 (CH_3); LRMS m/z 239 (M^+, 10), 211 (31), 208 (12), 196 (34), 180 (12), 165 (8), 164 (72), 154 (25), 152 (26), 136 (100), 125 (35), 108 (31), 96 (14), 94 (15), 56 (48), 55 (17); HRMS calcd for $C_{12}H_{17}O_4N$ 239.1158, found 239.115 88. **21** [R_f 0.48 (EtOAc), cryst. Et_2O mp 92−94 °C]: ^{1}H NMR δ 5.43 (1H, d, J = 5.5 Hz), 3.92 (1H, t, J = 5.7 Hz), 3.49 (3H, s), 3.39 (3H, s), 3.34 (1H, m), 2.12 (3H, s), 1.98 (2H, m), 1.12 (3H, s); ^{13}C NMR δ 196.0 (C), 172.1 (C), 151.1 (C), 109.0 (CH), 70.5 (C), 61.8 (CH), 54.9 (CH_3), 51.6 (CH_3), 46.1 (CH), 34.6 (CH_2), 32.1 (CH_3), 17.6 (CH_3); LRMS m/z 239 (M^+, 15), 211 (36), 196 (58), 180 (12),164 (73), 154 (28), 153 (11), 152 (54), 137 (14), 136 (100), 125 (26), 108 (29), 96 (13), 94 (18), 56 (59), 55 (16); HRMS calcd for $C_{12}H_{17}O_4N$ 239.1158, found 239.11585.

(1*R,5*R**,6*S**)-1,8-Dimethyl-3-methoxy-6-*exo*-(phenylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (18) and (1*R**,5*R**,6*R**)-1,8-Dimethyl-3-methoxy-6-*endo*-(phenylsulfonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (22).** 2,2,6,6-Tetramethylpiperidine (0.16 mL, 0.99 mmol) was added to a refluxing solution of **12** (200 mg, 0.66 mmol) and phenyl vinyl sulfone (570 mg, 3.3 mmol) in CH_3CN (6 mL). The mixture was refluxed overnight, poured into water, and extracted with CH_2Cl_2. The organic layer was dried and concentrated and the residue purified by flash chromatography (20−50% EtOAc/hexanes) to give 94 mg of compound **18** and 24 mg of **22** (total yield 58%). **18** [R_f 0.37 (EtOAc), white solid, mp 118−120 °C]: ^{1}H NMR δ 7.89 (2H, m), 7.57 (3H, m), 5.69 (1H, d, J = 5.3 Hz), 4.33 (1H, d, J = 5.5 Hz), 3.59 (3H, s), 3.52 (1H, dd, J = 3.8, 9.1 Hz), 2.30 (1H, dd, J = 3.9, 14.8 Hz), 2.15 (1H, dd, J = 9.1, 14.8 Hz), 2.11 (3H, s), 1.05 (3H, s); ^{13}C NMR δ 195.7 (C), 151.1 (C), 138.0 (C), 133.8 (CH), 129.1 (CH), 128.9 (CH), 109.8 (C), 69.8 (C), 67.3 (CH), 61.2 (CH), 55.1 (CH_3), 34.5 (CH_2), 30.8 (CH_3), 17.3 (CH_3); LRMS m/z 321 (M^+, 1.3), 278 (19), 152 (47), 137 (14), 136 (100), 125 (27), 108 (35), 96 (11), 94 (18), 82 (14), 77 (50); HRMS calcd for $C_{16}H_{19}O_4NS$ 321.10348, found 321.10332. **22** [R_f 0.24 (EtOAc), white solid, mp 107−109 °C]: ^{1}H NMR δ 7.85 (2H, m), 7.57 (3H, m), 5.85 (1H, d, J = 5.4 Hz), 4.19 (1H, t, J = 5.3 Hz), 4.05 (1H, ddd, J = 5.4, 6.9, 9.6 Hz), 3.72 (3H, s), 2.28 (3H, s), 2.25 (1H, dd, J = 6.9, 13.9 Hz), 2.01 (1H, dd, J = 9.6, 13.9 Hz), 1.26 (3H, s); ^{13}C NMR δ 195.3 (C), 151.3 (C), 140.1 (C), 133.9 (CH), 129.5 (CH), 127.8 (CH), 108.4 (CH), 70.8 (C), 65.9 (CH), 61.3 (CH), 55.2 (CH_3), 34.7 (CH_2), 31.6 (CH_3), 17.8 (CH_3); LRMS m/z 321(M^+, 6), 278 (14), 227 (13), 226 (88), 152 (28), 149 (17), 137 (17), 136 (100), 125 (80), 122 (17), 108 (29), 96 (21), 82 (17), 77 (52), 56 (32); HRMS calcd for $C_{16}H_{19}O_4NS$ 321.103 48, found 321.103 33.

3-[(Methoxymethylene)oxy]-2-methyl-4-pyrone (10c). Diisopropylethylamine (19 mL, 11.1 mmol) and MOMCl (6 mL, 9.9 mmol) were added to an ice-cooled solution of **10a** (7 g, 55.5 mmol). The mixture was stirred overnight at room temperature, poured into water, and extracted with CH_2Cl_2. The organic layer was dried and concentrated, and the residue was flash chromatographed (30−70% EtOAc/hexanes) to give 8.55 g of the pyrone **10c** [94%, R_f 0.38 (EtOAc), viscous oil]: ^{1}H NMR δ 7.61 (1H, d, J = 5.6 Hz), 6.33 (1H, d, J = 5.6 Hz), 5.17 (2H, s), 3.52 (3H, s), 2.35 (3H, s); ^{13}C NMR δ 174.4 (C), 159.2 (C), 153.7 (CH), 142.4 (C), 116.7 (CH), 96.9 (CH_2), 57.0 (CH_3), 14.5 (CH_3); LRMS m/z 170 (M^+, 2), 155 (23), 139 (26), 127 (130), 110 (100), 109 (15), 82 (10), 71 (11), 69 (34), 53 (19); HRMS calcd for $C_8H_{10}O_4$ 170.057 91, found 170.057 83.

1-Benzyl-3-hydroxy-2-methyl-4-pyridone (11c). Benzylamine (20 mL, 180 mmol) was added to a solution of **10c** (8 g, 47 mmol) in MeOH. The mixture was stirred for 3 days at room temperature, and more benzylamine (10 mL, 94 mmol) was added. After 4 days the solvent was evaporated and the remaining benzylamine removed under high vacuum. The residue (12.78 g) was directly subjected to the deprotection step, but a small fraction was purified by flash chromatography (0−10% MeOH/CH_2Cl_2) in order to complete its characterization. The expected product, **3-[(methoxymethylene)oxy]-1-benzyl-2-methyl-4-pyridone**, was obtained as a viscous red oil [98%, R_f 0.58 (EtOAc)]: ^{1}H NMR δ 7.36 (5H, m), 7.03 (1H, br d, J = 7.4 Hz), 6.45 (1H, d, J = 7.5 Hz), 5.29 (2H, s), 5.05 (2H, s), 3.52 (3H, s), 2.34 (3H, s); ^{13}C NMR δ 173.0 (C), 145.3 (C), 141.1 (C), 139.4 (CH), 135.4 (C), 129.2 (CH), 128.3 (CH), 125.9 (CH), 117.1 (CH), 97.2 (CH_2), 57.3 (CH_2), 56.9 (CH_3), 12.6 (CH_3); LRMS m/z 259 (M^+, 2), 244 (15), 199 (14), 91 (100); HRMS calcd for $C_{15}H_{17}O_3N$ 259.120 84, found 259.120 20.

A solution of 12 g of the residue obtained in the previous experiment in THF/H_2O (10:1, 22 mL) was stirred with HCl (10%, 1 mL) for 20 h at room temperature. The reaction mixture was carefully poured into a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried and concentrated and the residue crystallized from Et_2O/EtOAc (1:1) to afford 7.24 g of **11c** [72% from **10c**, R_f 0.44 (10% MeOH/CH_2Cl_2), white solid, mp 203−205 °C]: ^{1}H NMR [$(CD_3)_2$-

SO] δ 7.75 (1H, d, J = 7 Hz), 7.35 (3H, m), 7.07 (2H, m), 6.21 (1H, d, J = 7.1 Hz), 5.24 (2H, s), 2.11 (3H, s); ^{13}C NMR δ: 169.4 (C), 146.0 (C), 138.7 (CH), 137.2 (C), 129.1 (CH), 127.8 (CH), 126.2 (CH), 110.9 (CH), 56.1 (CH_2), 11.5 (CH_3); LRMS m/z 215 (M^+, 22), 91 (100), 57 (20); HRMS calcd for $C_{13}H_{13}O_2N$ 215.094 63, found 215.094 63. Anal. Calcd for $C_{13}H_{13}O_2N$: C, 72.526; H, 6.091; N, 6.510. Found: C, 72.61; H, 6.16; N, 6.57.

(1*R,5*R**,6*S**,7*S**)-1-Benzyl-8-methyl-3-methoxy-2-oxo-*N*-phenyl-8-azabicyclo[3.2.1]oct-3-ene-6,7-*exo*-dicarboximide (15).** Freshly distilled methyl trifluoromethanesulfonate (0.135 mL, 1.2 mmol) was added to a solution of **11c** (200 mg, 1 mmol) in $CHCl_3$ (50 mL). The mixture was refluxed for 3 h and the solvent evaporated under vacuum. The crude residue, a pale yellow solid, was found to consist mainly of the salt **1-benzyl-2-methyl-3-hydroxy-4-methoxypyridinium trifluoromethanesulfonate (13)** and was used in the cycloaddition reaction without further purification.

The cycloaddition of **13** to N-phenylmaleimide was carried out following the same procedure as for the preparation of **14**. Compound **15** (290 mg) was obtained as a white solid in 78% yield [R_f 0.42 (EtOAc/hexanes), mp 145−147 °C]: ^{1}H NMR δ 7.35 (10H, m), 5.8 (1H, d, J = 5.7 Hz), 4.21 (1H, d, J = 5.6 Hz), 3.85 (1H, d, J = 13.6 Hz), 3.67 (3H, s), 3.63 (1H, d, J = 13.6 Hz), 3.38 (1H, d, J = 7.3 Hz), 3.12 (1H, d, J = 7.3 Hz), 1.5 (3H, s); ^{13}C NMR δ 193.2 (C), 175.5 (C), 173.5 (C), 151.1 (C), 137.9 (C), 131.9 (C), 129.3 (CH), 128.9 (CH), 128.7 (CH), 127.8 (CH), 127.6 (CH), 126.4 (CH), 111.7 (CH), 72.4 (C), 57.9 (CH), 55.2 (CH_3), 51.4 (CH), 48.8 (CH), 47.8 (CH_2), 16.2 (CH_3); LRMS m/z (402, M^+, 1), 325 (10), 227 (10), 199 (24), 167 (26), 150 (19), 149 (100), 135 (31), 129 (23), 123 (15), 121 (17), 111 (23), 109 (16), 105 (43); HRMS calcd for $C_{24}H_{22}O_4N_2$ 402.157 96, found 402.157 53.

(1*R,5*R**,6*S**)-6-*exo*-Cyano-8-benzyl-8-methyl-3-methoxy-8-azabicyclo[3.2.1]oct-3-en-2-one (19) and (1*R**,5*R**,6*R**)-6-*endo*-Cyano-8-benzyl-1-methyl-3-methoxy-8-azabicyclo[3.2.1]oct-3-en-2-one (23).** The cycloaddition of **13** to acrylonitrile was carried out following the same procedure as for the preparation of **16** and **20**. Compounds **19** (91 mg) and **23** (84 mg) were obtained in 69% global yield. **19** [R_f 0.42 (50% EtOAc/hexanes), viscous oil]: ^{1}H NMR δ 7.28 (5H, m), 5.54 (1H, d, J = 5.4 Hz), 3.96 (1H, d, J = 5.4 Hz) 3.86 (1H, d, J = 13.9 Hz), 3.54 (1H, d, J =13.9 Hz), 2.85 (1H, dd, J = 4.8, 7.3 Hz), 2.32 (2H, m), 1.43 (3H, s); ^{13}C NMR δ 195.1 (C), 151.6 (C), 138.1 (C), 128.7 (CH), 128.0 (CH), 127.5 (CH), 121.6 (C), 109.3 (CH), 69.6 (C), 59.9 (CH), 55.2(CH_3), 47.9 (CH_2), 38.0 (CH_2), 31.1 (CH_3), 18.1 (CH_3); LRMS m/z 282 (M^+, 1), 191 (14), 172 (4), 167 (5), 149 (18), 91 (100); HRMS calcd for $C_{17}H_{18}O_2N_2$ 282.136 83 found 282.136 56. **23** [R_f 0.56 (50% EtOAc/hexanes), cryst Et_2O, mp 123−125 °C]: ^{1}H NMR δ 7.28 (m, 5H), 5.69 (1H, d, J = 5.5 Hz), 3.92 (1H, t, J = 5.5 Hz), 3.75 (1H, d, J = 13.2 Hz), 3.72 (3H, s), 3.55 (1H, d, J =13.2 Hz), 3.26 (1H, ddd, J = 5.6, 6.4, 10.2 Hz), 2.45 (1H, dd, J = 10.3, 13.9 Hz), 2.14 (1H, dd, J = 6.4, 13.9 Hz), 1.41 (3H, s); ^{13}C NMR δ: 194.9 (C), 152.2 (C), 137.9 (C), 128.7 (CH), 128.3 (CH), 127.6 (CH), 119.9 (C), 108.7 (CH), 70.0 (C), 57.6 (CH), 55.4 (CH_3), 48.5 (CH_2), 37.6 (CH_2), 30.6 (CH), 17.9 (CH_3); LRMS m/z 282 (M^+, 1), 191 (14), 149 (18), 104 (10), 91 (100), 64 (10); HRMS calcd for $C_{17}H_{18}O_2N_2$ 282.136 83, found 282.136 74.

2-(Hydroxymethylene)-5-[(*p*-methoxybenzyl)oxy]-4-pyrone (25). Potassium hydroxide (3.47 g, 61.9 mmol) was added to a solution of kojic acid (8 g, 56.3 mmol) in water (50 mL). The mixture was stirred until all the kojic acid had dissolved. The solvent was removed under vacuum to give 10.1 g of crude potassium kojate. Tetrabutylammonium iodide (24.5 g, 66.6 mmol) and *p*-methoxybenzyl chloride (9 mL, 66.6 mmol) were added to a suspension of the potassium kojate (8 g, 44.4 mmol) in acetone (150 mL). The mixture was heated under reflux for 18 h, cooled at room temperature, poured into water, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated. The residue was purified by flash chromatography (0−5% MeOH/CH_2Cl_2) to afford 11.4 g of **25** [98%, R_f 0.39 (EtOAc), white solid, cryst MeOH mp 119−121 °C]: ^{1}H NMR δ 8.12 (1H, s), 7.32 (2H, d, J = 8.2 Hz), 6.93 (2H, d, J = 8.2 Hz), 6.31 (1H, s), 5.67 (1H, t, J = 5.7 Hz), 4.84 (2H, s), 4.28 (2H, d, J = 5.4 Hz), 3.74 (3H, s); ^{13}C NMR δ 173.4 (C), 168.0 (C), 159.3 (C), 146.6 (C), 141.4 (CH), 129.9 (CH), 128.1 (C), 113.8 (CH), 111.2 (CH), 70.4 (CH_2), 59.3 (CH_2), 55.0 (CH_3); LRMS m/z 262 (M^+, 7), 122 (10), 121 (100); HRMS calcd for $C_{14}H_{14}O_5$ 262.084 12, found 262.084 56. Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.117; H, 5.380. Found: C, 64.32; H, 5.47.

2-[(Allyloxy)methylene]-5-[(*p*-methoxybenzyl)oxy]-4-pyrone (26). A potassium fluoride/alumina mixture (40%, 8.3 g, 57.3 mmol) and allyl bromide (20 mL, 22.8 mmol) were added to a solution of **25** (3 g, 11.4 mmol) in CH_3CN (25 mL). The resulting suspension was refluxed for 22 h and filtered, and the solids were rinsed with EtOAc. The filtrate was concentrated and the residue chromatographed (20−40% EtOAc/hexanes) to give 2.98 g of **26** [86%, R_f 0.43 (50% EtOAc/hexanes), white solid, mp 43−45 °C]: ^{1}H NMR δ 7.01 (1H, d, J = 8.7 Hz), 6.87 (1H, s), 6.51 (1H, d, J = 8.7 Hz), 6.08 (1H, s), 5.55 (1H, m), 4.95 (2H, m), 4.67 (2H, s), 3.95 (2H, s), 3.66 (2H, d, J = 6.9 Hz), 3.43 (3H, s), 3.26 (3H, s); ^{13}C NMR δ: 174.6 (C), 164.0 (C), 159.7 (C), 147.0 (C), 141.7 (CH), 133.5 (CH), 129.6 (CH), 127.8 (C), 118.0 (CH_2), 113.9 (CH), 113.4 (CH), 71.95 (CH_2), 71.95 (CH_2), 71.46 (CH_2), 67.4 (CH_2), 55.1 (CH_3); LRMS m/z 302 (M^+, 4), 151 (4), 121 (100), 95 (4); HRMS calcd for $C_{17}H_{18}O_5$ 302.115 424, found 302.1152. Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.539; H, 6.001. Found: C, 67.49; H, 5.87.

2-[(Allyloxy)methylene]-5-hydroxy-1-methyl-4-pyridone (27). Aqueous methylamine (40%, 5 mL, 58 mmol) was added to a solution of **26** (2.5 g, 8.2 mmol) in EtOH (20 mL). The mixture was stirred overnight at room temperature and the solvent removed under reduced pressure. The crude was partitioned between water and CH_2Cl_2, and the combined organic extracts were dried and concentrated. The residue (2.7 g) was directly subjected to the deprotection step, but a small amount was purified by flash chromatography (0−10% MeOH/CH_2Cl_2) in order to characterize the product: **2-[(allyloxy)methylene]-5-[(*p*-methoxybenzyl)oxy]-1-methyl-4-pyridone** [R_f 0.72 (10% MeOH/CH_2Cl_2), red oil]: ^{1}H NMR δ 7.01 (1H, d, J = 8.7 Hz), 6.87 (1H, s), 6.51 (1H, d, J = 8.7 Hz), 6.08 (1H, s), 5.55 (1H, m), 4.95 (2H, m), 4.67 (2H, s), 3.95 (2H, s), 3.66 (2H, d, J = 6.9 Hz), 3.43 (3H, s), 3.26 (3H, s); ^{13}C NMR δ 172.6 (C), 159.3 (C), 147.9 (C), 144.0 (C), 133.4 (CH), 129.4 (CH), 128.8 (C), 117.8 (CH), 117.8 (CH_2), 113.6 (CH_2), 71.0 (CH_2), 70.9 (CH_2), 67.8 (CH_2), 54.9 (CH_3), 40.0 (CH_3); LRMS m/z 315 (M^+, 42), 179 (17), 122 (11), 121 (100); HRMS calcd for $C_{18}H_{21}O_4N$ 315.1470 58, found 315.1475 53.

Trifluoroacetic acid (2 mL, 30 mmol) was added to a solution of part of the residue obtained in the previous experiment (2 g, 6.3 mmol) in CH_2Cl_2 (18 mL). The mixture was stirred for 6 h at room temperature and the solvent evaporated under vacuum. The crude was crystallized from CH_2Cl_2 to give 962 mg of **27** [80% from **26**, R_f 0.55 (10% MeOH/CH_2Cl_2), white solid, mp 185 °C]: ^{1}H NMR δ 11.09 (1H, br s), 8.25 (1H, s), 7.32 (1H, s), 5.95 (1H, m), 5.22 (2H, m), 4.72 (2H, s), 4.13 (2H, d, J = 6.8 Hz), 4.11 (3H, s); ^{13}C NMR δ 164.2 (C), 147.3 (C), 146.6 (C), 135.1 (CH), 133.4 (CH), 118.1 (CH_2), 114.4 (CH), 72.4 (CH_2), 67.8 (CH_2), 43.1 (CH_3); LRMS m/z 195 (M^+, 61), 153 (10), 139 (55), 138 (29), 111 (14), 110 (100), 69 (28), 67 (13), 55 (10); HRMS calcd for $C_{10}H_{13}O_3N$ 195.080 990, found 195.090 201. Anal. Calcd for $C_{14}H_{15}O_2N$: C, 61.510; H, 6.716; N, 7.178. Found: C, 61.63; H, 6.89; N, 7.21.

2-[(Allyloxy)methylene]-5-[(*tert*-butyldimethylsilyl)oxy]-1-methyl-4-pyridone (28). To a solution of **6** (200 mg, 1 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (108 μl, 1.5 mmol), *t*-butyldimethylsilyl chloride (240 mg, 1.5 mmol), and a catalytic amount of DMAP. The mixture was stirred at room temperature for 30 min, poured into brine, and extracted with CH_2Cl_2. The organic layers were dried, filtered, and concentrated. The residue was chromatographed on neutral alumina (deactivated with 6% H_2O) to afford 292 mg of **28** [93%, R_f 0.78 (EtOAc), viscous oil]: ^{1}H NMR δ 7.27 (1H, s), 6.5 (1H, s), 5.97 (1H, m), 5.28 (2H, m), 4.78 (2H, s), 4.23 (2H, d, J = 6.4 Hz), 4.2 (3H, s), 0.89 (9H, s), 0.24 (6H, s).

9-Methoxy-11-methyl-8-oxo-11-azatricyclo[5.3.1.0^{1,5}]undec-9-ene (29). Methyl trifluoromethansulfonate (0.135 μL, 1.2 mmol) was added to a solution of **27** (200 mg, 1 mmol) in $CHCl_3$ (25 mL). The mixture was refluxed for 3 h and concentrated, and the residue was dried under high vacuum for 5 h. 2,2,6,6-Tetramethylpiperidine (0.260 mL, 1.5 mmol)

was added to a solution of this crude salt (378 mg) in CH_3CN (60 mL), and the mixture was heated in a sealed tube at 110 °C overnight. The solvent was evaporated and the residue chromatographed on silica gel (50−100% EtOAc/hexanes) to afford 197 mg of the cycloadduct **29** [92% R_f (EtOAc), white solid, mp 86−89 °C]: ^{1}H NMR [$(CD_3)_2CO$] δ 5.9 (1H, s), 4.07 (1H, t, J = 8 Hz), 3.88 (2H, dd, J = 15.4 Hz), 3.61 (2H, m), 3.57 (3H, s), 2.76 (1H, ddd, J = 14.2, 8.6, 5.3 Hz), 2.27 (3H, s), 2.07 (1H, m), 1.55 (1H, dd, J = 13.3, 8.6 Hz); ^{13}C NMR [$(CD_3)_2$-CO] δ 194.8(C), 153.0 (C), 113.8 (CH), 75.6 (CH), 75.3 (C), 75.1 (CH_2), 73.4 (CH_2), 55.2 (CH_3), 53.4 (CH_3), 31.7 (CH_3), 28.0 (CH_2); LRMS m/z 209 (M^+, 47), 181 (39), 167 (12), 166 (100), 150 (63), 138 (30), 109 (46); HRMS calcd for $C_{11}H_{15}O_3N$ 209.105 19, found 209.105 19.

Acknowledgment. We thank the DGICYT (Spain) and the Xunta de Galicia for financial support under projects SAF 92-0572, SAF 95-0878, and XUGA 20901A94. A.R. also thanks the Xunta de Galicia for a fellowship.

Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra for **4**−**6**, **11c**, **12**, **14**−**23**, **26**, **27**, and **29** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960854V