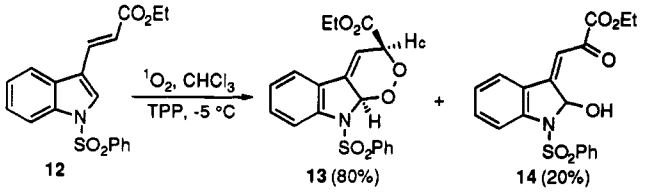
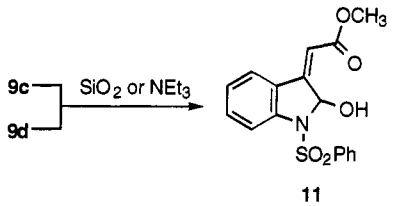
Scheme IV



nearly identical. Two peroxy carbons were found at 92.4 and 72.0 ppm, respectively. Neither trimethyl phosphite nor thiourea reduces the peroxide bond.

Putting a methyl group with abstractable allylic hydrogens on the α-position of the 3-vinyl double bond allows the ene reaction to compete with endoperoxide formation. Also, the α-methyl should activate the double bond, resulting in increased [2 + 2] cycloaddition reactivity. Careful examination of the reaction of 1-(phenylsulfonyl)-3-(2-propenyl)indole (**8b**) with $^1O_2$ with ^1H NMR showed no ene product. Endoperoxide **9b** (85%) and cleaved ketone **10b** (15%, the precursor for **8b**) were produced. Endoperoxide **9b** was isolated and characterized by spectroscopic methods.

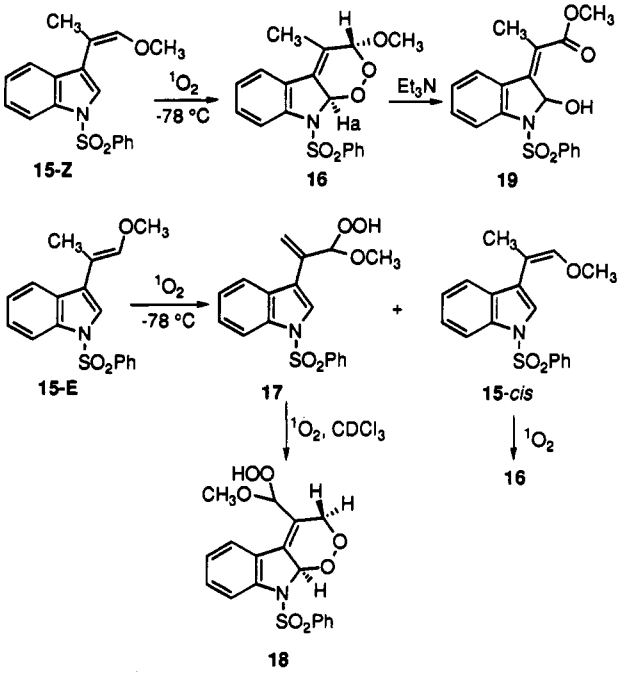
For comparison, we synthesized isomerically pure 1-(phenylsulfonyl)-3-(β-methoxyvinyl)indole (**8c** and **8d**).[38] Photooxygenation of **8c** in $CDCl_3$ at −5 °C gave endoperoxide **9c** in almost quantitative yield, while photooxygenation of **8d** produced 93% **9d** and 7% of the [2 + 2] cleavage product, **10**. Unlike **5**, which rearranges to epoxide **7**, endoperoxide **9c** and **9d** are fairly stable at room temperature and slowly rearrange to 1-(phenylsulfonyl)-2-hydroxy-3-[(methoxycarbonyl)methylene]indoline (**11**). This process was accelerated by SiO_2 or triethylamine, which converted **9c** and **9d** completely to **11** (Kornblum–DeLaMare rearrangement[39]). IR of hydroxyindoline **11** shows a characteristic strong OH band at 3483 cm^{-1} and an α,β-unsaturated ester carbonyl band at 1700 cm^{-1}.



Photooxygenation of 1-(Phenylsulfonyl)-3-[(β-ethoxycarbonyl)vinyl]indole (12). Photooxygenation of the electron-poor diene **12** in $CHCl_3$ produced a mixture of endoperoxide **13**, characterized by ^1H NMR, and hydroxyindoline **14** in a 4:1 ratio (Scheme IV). This reaction is very slow (complete conversion of **12** requires 6 h compared to 40 min for other 3-vinylindoles), and rearrangement of **13** to **14** is much faster than in the other cases, undoubtedly due to the increased acidity of H_c. The slow photooxygenation is also a result of the low electron density of the diene system caused by the ester and phenylsulfonyl substitution.

Photooxygenation of 1-(Phenylsulfonyl)-3-(α-methyl-β-methoxylvinyl)indole (15). To study the effect of methyl and methoxyl groups on the photooxygenation further, we prepared 1-methyl-3-(α-methyl-β-methoxyvinyl)indole (**15**). The *Z*- and *E*-isomers were separated by HPLC. The two isomers react completely differently with $^1O_2$. Like most 3-vinylindoles above, the *Z*-isomer gave exclusively endoperoxide **16** via [4 + 2] cycloaddition. In contrast, the *E*-isomer gave 87% of the ene product hydroperoxide, **17**, and 13% isomerization to **15-*Z***(Scheme V). Further photooxygenation converted **15-*Z*** and hydroperoxide **17** to the corresponding endoperoxides **16** and hydroperoxyendoperoxide **18**, respectively. Endoperoxide **16** was recrystallized from CH_2Cl_2/hexane (1:1) and characterized by spectroscopic methods and X-ray crystallography (Figure 1). The *cis* relationship of H_a and the OCH_3 is obvious. Endoperoxide **16** could also be easily converted to hydroxyindoline **19**, which shows strong bands at 3487 cm^{-1} for OH and 1707 cm^{-1} for ester carbonyl. Hydroperoxide **17** was isolated by TLC, and ^1H NMR showed an OOH signal at 8.54 ppm as a broad peak. ^{13}C NMR revealed a methine carbon at 108.0 ppm, assigned to the hydroperoxy carbon. IR showed a strong peak at 3428 cm^{-1}. Hydroperoxyendoperoxide **18** was also isolated and fully characterized. DEPT spectra show two CHs at 104.1 and 91.7 and a CH_2 at 70.7 ppm, respectively.

Scheme V



Discussion

Endoperoxidation is the preferred process in the singlet oxygenation of nonhomoannular dienes.[40] Only when tri- or tetrasubstituted double bonds with accessible allylic hydrogens are present does the ene reaction become dominant and even then, not always.[41] In alkenylaromatic and related systems, even with two β-methyl groups present, endoperoxidation is the favored reaction.[42–46] Our

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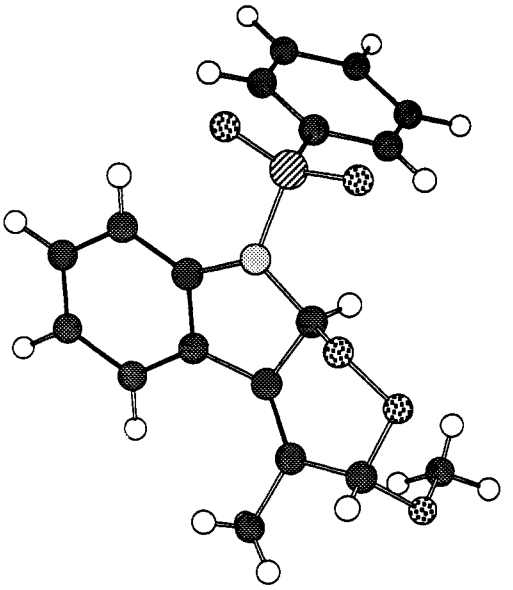


Figure 1. X-ray crystal structure of 16.

Table I. Sensitized Photooxygenation of *N*-Substituted 3-Vinylindole Derivatives

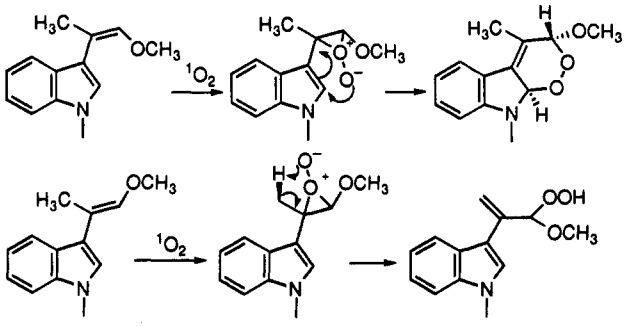
	relative yield,[a] %		
substrate	endoperoxidation	[2 + 2] cycloaddition	ene reaction
1a	>98	0	*d*
1b	93	7	*d*
1c[b]	0	>90	*d*
4-*Z*[c]	>98	0	*d*
4-*E*	92	8	*d*
8a	>98	0	*d*
8b	85	15	0
8c	>98	0	*d*
8d	93	7	*d*
15-*Z*	>98	0	0
15-*E*[e]	0	0	85

[a] Determined by ^{1}H NMR (360 MHz). [b] ^{1}H NMR was taken at −78 °C. Minor products formed in about 10% yield have not been identified. [c] ^{1}H NMR was done at −45 °C. [d] Ene reaction impossible. [e] 13% isomerization to 15-*Z*.

results with 3-vinylindole derivatives parallel this trend (Table I). However, an α-methyl substituent leads to exclusive formation of allylic hydroperoxides in the naphthalene[43] and phenanthrene[44] series. In contrast, an α-methyl substituent in 3-vinylindole **8b** is not sufficient to allow the ene reaction to compete with [4 + 2] cycloaddition, probably because the diene in the 3-vinylindole system is more reactive than that in the naphthalene or phenanthrene series. ^{1}H and ^{13}C NMR studies on selected 3-vinylindoles suggest that they have the π-electron density of a 1-aminobutadiene incorporated in a heterocyclic framework.[31,47] He(I) PE spectra show a first vertical ionization potential of about +7 eV for most 3-vinylindoles, and SCF-MO calculation has shown that [4 + 2] cycloaddition of α-donor-substituted 3-vinylindoles proceeds under $HOMO_{diene}$–$LUMO_{dienophile}$ control, like most Diels–Alder reactions.[31,48]

Introduction of a β-methoxy group into α-methylstyrenes has been shown to have a dramatic effect on the mode of reaction, directing attack of $^1O_2$ to the group *cis*

Scheme VI



to itself.[49,50] This directing effect of a methoxy group is also observed in the 3-vinylindole system, as shown by the reactions of **15-*Z*** and **15-*E*** suggesting that this is a general phenomenon. Also, *Z*-isomers (**4-*Z*** and **8c**) always give a higher yield of endoperoxide than *E*-isomers (**4-*E*** and **8d**). Competition kinetic studies at −45 °C indicated that the ratio of the rate constant of the *Z*-isomer to that of the *E*, k_Z/k_E is 4.1 when R is methyl and 5.2 when R is phenylsulfonyl. In both cases, the *Z*-isomer is faster.

The results of this study together with those from the styrene system are in agreement with previous suggestions that a perepoxide or exciplex is intermediate in this reaction. The methoxy group directs the incoming $^1O_2$ *cis*, as shown in Scheme VI.

The isomerization in the photooxygenation of **15-*E*** is extremely important. This isomerization was not caused by incidental UV light, since irradiation of the reaction under argon gave no isomerization and since $^1O_2$ generated by thermolysis of 9,10-dimethylnaphthalene endoperoxide[51] also gave 17% isomerization. There are several examples of substantial *cis/trans* isomerization in the photooxygenation of substituted butadienes.[19,52–54] The formation of the **15-*Z*** isomer can most easily be explained by invoking a freely-rotating zwitterion intermediate[19,52,55–58] (Scheme VII).

Two experiments were conducted to obtain more information about intermediates in this reaction. Photooxygenation of **15-*E*** at −95 °C in CD_2Cl_2 with 1.5 equiv of trimethyl phosphite[59,60] did not give epoxide **20**. Instead, aldehyde **21** was obtained in high yield. Controls showed that trimethyl phosphite reduced allylic hydroperoxide **17** quantitatively to **21**. Secondly, attempts to trap zwitterion **22b** with the nucleophilic solvent methanol failed to give adduct **23**. The product distribution in methanol is essentially the same as in CH_2Cl_2. Also, no transient absorption corresponding to zwitterion **22b** could be detected by flash photolysis between 400 and 700 nm.

(46) Goto, T.; Nakamura, H. *J. Chem. Soc., Chem. Commun.* **1978**, 781–782.
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(53) Clennan, E. L.; L'Esperance, R. P.; Lewis, K. K. *J. Org. Chem.* **1986**, *51*, 1440–1446.
(54) Clennan, E. L.; Nagraba, K. *J. Org. Chem.* **1987**, *52*, 294–296.
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(57) Kwon, B.-M.; Foote, C. S.; Khan, S. I. *J. Org. Chem.* **1989**, *54*, 3378–3382.
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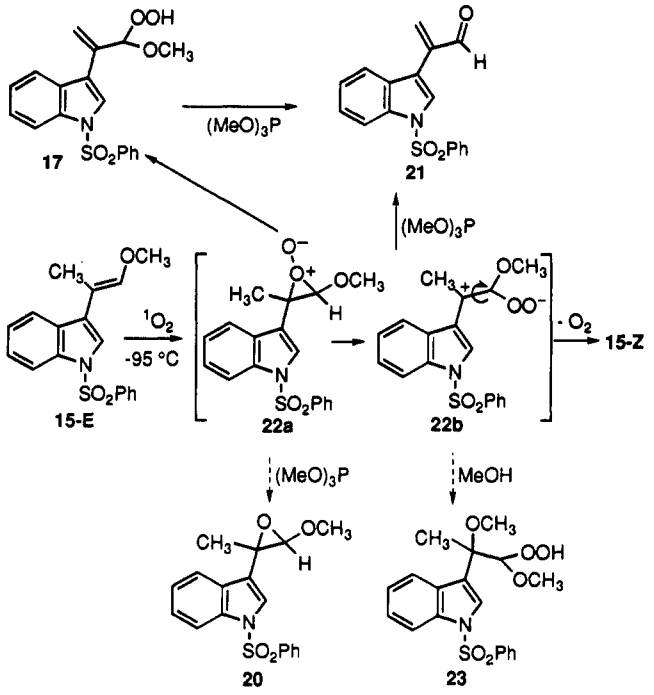
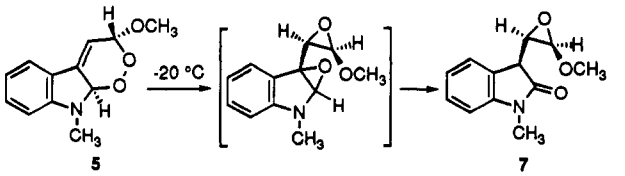
(60) Nahm, K.; Foote, C. S. *J. Am. Chem. Soc.* **1989**, *111*, 1909–1910.

Scheme VII



Scheme VIII



some *N*-(phenylsulfonyl) endoperoxides such as **9a** and **9b** are isolable by TLC. 1-(Phenylsulfonyl) endoperoxides **9c**, **9d**, and **13** undergo Kornblum–DeLaMare rearrangement[39] on SiO_2 instead of cleaving the 3-vinyl double bond. In other words, the stability and products of reaction of the endoperoxide are governed not only by the nitrogen substituent but also by the 3-vinyl β-substituent. Electron-withdrawing substituents on the *N* stabilize the resulting endoperoxide; on the β carbon, they destabilize it and favor Kornblum–DeLaMare rearrangement. However, the stereochemical factors governing these processes are not yet clear.

Even though these experiments did not give positive evidence for zwitterion **22b**, this species is still the likely intermediate.

Not suprisingly, the photooxygenation rate of 1-methyl-3-(β-methoxyvinyl)indole **4-*E*** is five times faster than that of 1-(phenylsulfonyl)-3-(β-methoxyvinyl)indole (**8d**). This difference is a result of the electronic effect of the phenylsulfonyl group, which decreases the diene reactivity. The electronic effect also explains the slow photooxygenation rate of 1-(phenylsulfonyl)-3-[(β-ethoxycarbonyl)-vinyl]indole (**12**).

Formation of indolin-2-one epoxide **7** from rearrangement of *trans*-endoperoxide **5** can be rationalized by formation of an intermediate diepoxide (Scheme VIII). ^1H NMR gave no evidence for a diepoxide intermediate at −20 °C. However, other *N*-acylindole 2,3-epoxides have been observed at low temperature and rearrange easily to indolinones by hydride or alkyl shift.[26] Thermal rearrangement of endoperoxides to diepoxides is a general process,[61] well known in cyclopentadiene[62,63] and cyclohexadiene endoperoxides.[64,65] Why *cis* endoperoxide **6** is so much more stable than *trans*-**5** is not clear at this stage.

In the initial studies of the sensitized photooxygenation of 1-methyl-3-vinylindoles,[29] Matsumoto proposed that an initial endoperoxide may rearrange to a dioxetane which then cleaves. Our results support this suggestion only when methyl is attached to the nitrogen. For example, endoperoxide **2b** was completely converted to **3b** on TLC, and endoperoxide **6** slowly rearranged to **3b** on SiO_2. Rearrangement of an endoperoxide to a dioxetane was also reported in the dye-sensitized photooxygenation of 2-alkoxyoxazoles[66] and an acyl furan.[67] On the other hand,

Conclusions

N-Substituted 3-vinylindole derivatives undergo photooxidation with $^1O_2$ efficiently and stereospecifically to dioxacarbazole endoperoxides in most cases. Some of the endoperoxides are stable and isolable under neutral conditions and inert to reduction by trimethyl phosphite or thiourea. *N*-Methyl-substituted endoperoxides are especially sensitive to acid and rearrange to dioxetanes which cleave the 3-vinyl double bond. *N*-(Phenylsulfonyl) endoperoxides are more stable than their *N*-methyl counterparts. They undergo Kornblum–DeLaMare rearrangement[39] upon treatment with base (Et_3N) or acid (SiO_2). β-Methoxy substituents have a strong directing effect on the reaction, not only making the ene reaction occur exclusively when a *cis* α-methyl is also present, but also accelerating the endoperoxidation when the aromatic double bond is *cis*. [2 + 2] Cycloaddition occurs at the 3-vinyl double bond preferentially when the s-*cis* conformation is blocked by substituents at the 2 and β-positions. Besides the important mechanistic aspects revealed by the variations in reaction type of the 3-vinylindole derivatives, the rich chemistry of the resulting peroxides[68] can also be used to prepare a variety of other indole derivatives which may be difficult to obtain with other methods.

Experimental Section

General. Melting points were determined on a MEL-TEMP aparatus and are uncorrected. ^1H and ^{13}C NMR were recorded on Bruker AM-360 or AM-500 instruments. Unless otherwise noted, NMR spectra were taken in $CDCl_3$, and chemical shifts are expressed in ppm (δ) relative to TMS. Multiplicity of carbon signals was determined by DEPT experiments. IR spectra were recorded on a Nicolet FT-205 spectrophotometer. EI-HRMS spectra were determined on an AEI MS-902 spectrometer. FAB mass spectra were obtained on an AEI MS-9 spectrometer. All samples submitted for exact mass determination were shown to be >95% pure by ^1H NMR analysis. Flash column chromatography was carried out on SiO_2 (silica gel 60, 40–63 μm). HPLC

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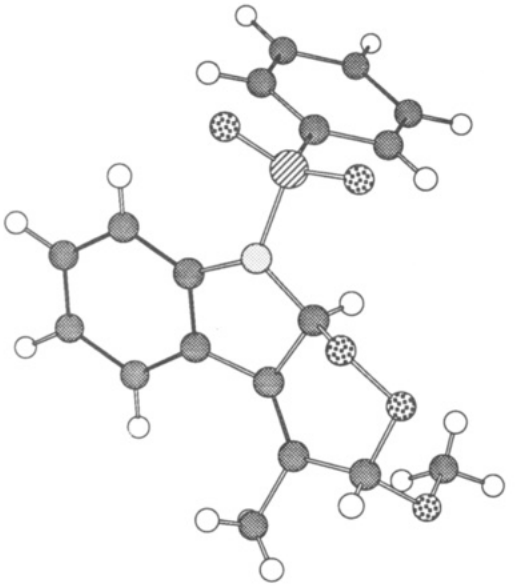

Figure 1. X-ray crystal structure of **16**.

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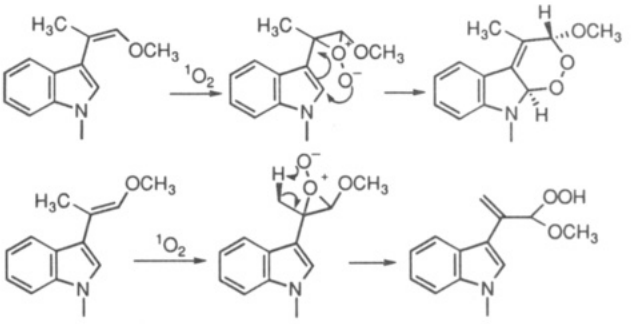
Scheme VI



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(60) Nahm, K.; Foote, C. S. *J. Am. Chem. Soc.* **1989**, *111*, 1909–1910.

Stirring was continued at −78 °C for 2 h and at room temperature for another 30 min. The mixture was quenched with saturated NH_4Cl solution, extracted with Et_2O, dried with Na_2SO_4, and purified by flash column chromatography (CH_2Cl_2:petroleum ether = 2.5:4) to give 2.1 g (45%) of a mixture of **15-*Z*** and **15-*E***. The pure isomeric material was obtained by HPLC with a 250-× 22.5-mm C_{18} Econosil column at a flow rate of 10 mL/min (mobile phase, H_2O:MeOH = 25:75): mp 83–84 °C for **15-*Z***; ^1H NMR (CD_2Cl_2) δ 7.98 (d, 1 H, J = 8.26 Hz), 7.90 (d, 2 H, J = 8.23 Hz), 7.71 (s, 1 H), 7.69 (d, 1 H, J = 7.92 Hz), 7.54 (t, 1 H, J = 7.42 Hz), 7.46 (t, 2 H, J = 8.24 Hz), 7.30 (t, 1 H, J = 7.46 Hz), 7.23 (t, 1 H, J = 7.47 Hz), 6.15 (q, 1 H, J = 1.32 Hz), 3.68 (s, 3 H), 2.02 (d, 3 H, J = 1.48 Hz); ^{13}C NMR (CD_2Cl_2) δ 145.29, 138.51, 135.32, 134.26, 130.40, 129.69, 127.17, 124.76, 124.55, 123.34, 122.92, 121.53, 113.77, 104.55, 60.30, 18.96; IR (NaCl, CD_2Cl_2) cm^{-1} 2950 (w), 1650 (w), 1450 (s), 1360 (s), 1180 (s), 1160 (s), 1060 (m), 950 (w).

15-*E*: mp 82–83 °C; ^1H NMR (CD_2Cl_2) δ 8.00 (d, 1 H, J = 8.14 Hz), 7.89 (d, 2 H, J = 8.20 Hz), 7.68 (d, 1 H, J = 7.84 Hz), 7.54 (t, 1 H, J = 7.32 Hz), 7.47 (t, 2 H, J = 8.10 Hz), 7.44 (s, 1 H), 7.32 (d, 1 H, J = 7.46 Hz), 7.26 (t, 1 H, J = 7.78 Hz), 6.60 (q, 1 H, J = 1.26 Hz), 3.73 (s, 3 H), 2.01 (d, 3 H, J = 1.32 Hz); ^{13}C NMR (CD_2Cl_2) δ 146.46, 138.38, 136.06, 134.26, 129.68, 129.47, 127.11, 125.12, 123.96, 123.80, 122.18, 121.53, 114.21, 107.39, 60.37, 13.52; IR (NaCl, CD_2Cl_2) cm^{-1} 2948 (w), 1650 (m), 1439 (s), 1350 (s), 1210 (s), 1160 (s), 1120 (s), 1080 (m), 950 (m), 750 (s).

9,9a-Dihydro-9-methyl-3*H*-1,2-dioxino[3,4-*b*]indole (2a). Compound **1a** (60 mg, 0.38 mmol) was combined with a few milligrams of polymer-bound rose bengal (P–RB) in 5 mL of CH_2Cl_2. Photooxygenation was carried out at −78 °C for 1.0 h. The sensitizer was removed by filtration, and the filtrate was condensed; ^1H NMR showed endoperoxide **2a** was present (>97%). Recrystallization from 5:1 petroleum ether/CH_2Cl_2 resulted in 57 mg (80%) pure **2a**: mp 79–80 °C (lit.[45] mp 80–82 °C); ^1H NMR (CD_2Cl_2) δ 7.26 (d, 1 H, J = 7.36 Hz), 7.17 (t, 1 H, J = 7.88 Hz), 6.78 (t, 1 H, J = 7.48 Hz), 6.59 (d, 1 H, J = 7.93 Hz), 5.90 (q, 1 H, J = 2.57 Hz), 5.84 (q, 1 H, J = 2.30 Hz), 5.01 (dt, AB, 1 H, J_{AB} = 16.79 Hz, J_t = 2.61 Hz), 4.63 (dt, AB, 1 H, J_{AB} = 16.74 Hz, J_t = 2.76 Hz), 2.88 (s, 3 H); COSY was performed to find the coupling pattern; ^{13}C NMR (CD_2Cl_2) δ 152.46 (s), 136.78 (s), 130.39 (d), 125.34 (s), 121.13 (d), 120.10 (d), 114.24 (d), 108.97 (d), 98.99 (d), 71.41 (t), 35.11 (q).

9,9a-Dihydro-9,9a-dimethyl-3*H*-1,2-dioxino[3,4-*b*]indole (2b). Compound **1b** (20 mg, 0.12 mmol) was combined with P–RB in 0.5 mL of $CHCl_3$ in a 5-mm NMR tube. Photooxygenation was done at −5 °C for 1.0 h. ^1H NMR indicated that **1b** was completely converted and 93% of **2b** and 7% of aldehyde **3b** were present. P–RB was removed by filtration, and the filtrate was condensed. Adding several drops of 5:1 ether/pentane induced precipitation of **2b** (14 mg, 60%): ^1H NMR (CD_2Cl_2) δ 7.24 (d, 1 H, J = 7.34 Hz), 7.14 (t, 1 H, J = 7.76 Hz), 6.74 (t, 1 H, J = 7.50 Hz), 6.49 (d, 1 H, J = 7.89 Hz), 5.76 (t, 1 H, J = 2.67 Hz), 4.99 (dd, ABX, 1 H, J_{AB} = 16.75 Hz, J_X = 2.50 Hz), 4.57 (dd, ABX, 1 H, J_{AB} = 16.76 Hz, J_X = 2.82 Hz), 2.80 (s, 3 H), 1.66 (s, 3 H): ^{13}C NMR (CD_2Cl_2) δ 153.03 (s), 136.98 (s), 130.06 (d), 124.91 (s), 121.01 (d), 119.35 (d), 112.80 (d), 107.91 (d), 105.41 (s), 70.58 (t), 29.69 (q), 18.06 (q). IR (NaCl, CD_2Cl_2) cm^{-1} 3080 (w), 2880 (m), 1648 (s), 1611 (s), 1469 (m), 865 (w), 840 (w), 744 (m); MS m/z 203 (M, 11.3), 187 (20), 172 (100), 158 (55), 149 (30), 136 (36), 125 (60); HRMS calcd for $C_{12}H_{13}NO_2$ 203.0947, obsd 203.0945.

Photooxygenation of 1c. Compound **1c** (80 mg, 0.40 mmol) was combined with P–RB in 5 mL of CH_2Cl_2. Photooxygenation was carried out at −78 °C for 2 h. Sensitizer was removed by filtration. ^1H NMR of the crude reaction mixture showed that most (>90%) of the product was aldehyde **3c**: ^1H NMR ($CDCl_3$) δ 10.03 (s, 1 H), 8.19 (d, 1 H, J = 7.82 Hz), 7.22–7.17 (m, 3 H), 3.54 (s, 3 H), 2.52 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 183.94 (d), 148.00 (s), 136.92 (s), 125.54 (s),122.96 (d), 122.64 (d), 120.73 (d), 114.05 (s), 109.16 (d), 29.49 (q), 10.38 (q).

trans*-9,9a-Dihydro-3-methoxy-9-methyl-3*H*-1,2-dioxino-[3,4-*b*]indole (5).** Compound **4-*Z (51 mg, 0.27 mmol) was combined with TPP in 0.5 mL of CD_2Cl_2 in a 5-mm NMR tube and photooxygenated at −78 °C for 40 min. ^1H NMR at −45 °C showed that all **4-*Z*** had reacted and that endoperoxide **5** was the only product: ^1H NMR (CD_2Cl_2, −45 °C) δ 7.33 (d, 1 H, J = 7.38 Hz), 7.24 (t, 1 H, J = 7.84 Hz), 6.82 (t, 1 H, J = 7.39 Hz), 6.65 (d, 1 H, J = 7.96 Hz), 5.83 (t, 1 H, J = 2.07 Hz), 5.80 (t, 1 H, J = 2.31 Hz), 5.77 (t, 1 H, J = 2.48 Hz), 3.52 (s, 3 H), 2.88 (s, 3 H), ^{13}C NMR (CD_2Cl_2, −45 °C) δ 152.21 (s), 142.07 (s), 131.20 (d), 123.52 (s), 121.64 (d), 119.95 (d), 113.64 (d), 109.22 (d), 101.82 (d), 98.11 (d), 56.51 (q), 34.88 (q).

Endoperoxide **5** started to rearrange at −20 °C, and rearrangement was complete in 10 min when the probe temperature reached 0 °C. ^1H NMR showed that the rearrangement is very clean. An analytical sample of epoxide **7** was obtained by recrystallization from ether: ^1H NMR ($CDCl_3$) δ 7.33 (d, 1 H, J = 7.20 Hz), 7.27 (d, 1 H, J = 7.80 Hz), 7.05 (t, 1 H, J = 7.48 Hz), 6.82 (t, 1 H, J = 7.75 Hz), 4.66 (d, 1 H, J = 2.67 Hz), 3.66 (d, 1 H, J = 8.68 Hz), 3.64 (s, 3 H), 3.24 (s, 3 H), 2.97 (dd, 1 H, J = 8.68, 2.69 Hz); ^{13}C NMR ($CDCl_3$) δ 175.47 (s), 144.55 (s), 128.81 (d), 125.28 (d), 124.49 (s), 122.51 (d), 108.04 (d), 80.00 (d), 56.93 (q), 56.46 (d), 45.01 (d), 26.29 (q); IR (NaCl, $CDCl_3$) cm^{-1} 2900 (w), 3000 (w), 1702 (s), 1613 (s), 1494 (m), 977 (m), 843 (m), 753 (m), 733 (m); MS m/z 219 (M, 54), 204 (26), 174 (100), 159 (52), 146 (80), 130 (50), 117 (38); HRMS calcd for $C_{12}H_{13}NO_3$ 219.0896, obsd 219.0895.

cis*-9,9a-Dihydro-3-methoxy-9-methyl-3*H*-1,2-dioxino[3,4-*b*]indole (6).** Compound **4-*E (42 mg, 0.22 mmol) was combined with TPP in 2 mL of $CHCl_3$ and photooxygenated at −5 °C for 30 min. ^1H NMR of the crude product showed 92% of **6** and 8% of aldehyde **3b**. An analytical sample of **6** was obtained by precipitation of **6** from 5:1 petroleum ether/acetone: ^1H NMR ($CDCl_3$) δ 7.28 (d, 1 H, J = 7.30 Hz), 7.21 (t, 1 H, J = 6.94 Hz), 6.79 (t, 1 H, J = 7.50 Hz), 6.59 (d, 1 H, J = 7.95 Hz), 5.79 (t, 1 H, J = 2.41 Hz), 5.77 (t, 1 H, J = 2.30 Hz), 5.34 (t, 1 H, J = 1.90 Hz), 3.58 (s, 3 H), 2.93 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 152.69 (s), 141.36 (s), 131.12 (d), 123.57 (s), 121.69 (d), 119.80 (d), 111.61 (d), 108.64 (d), 99.48 (d), 97.48 (d), 55.84 (q), 34.53 (q); IR (NaCl, $CDCl_3$) cm^{-1} 2951 (w), 1607 (m), 1490 (s), 1371 (m), 1332 (m), 1090 (s), 1061 (s), 970 (m), 914 (m), 853 (m), 801 (m); MS m/z 220 (M + 1, 3), 219 (M, 16), 203 (2), 187 (6), 174 (20), 160 (40), 159 (100); HRMS calcd for $C_{12}H_{13}NO_3$ 219.0896, obsd 219.0895.

9,9a-Dihydro-9-(phenylsulfonyl)-3*H*-1,2-dioxino[3,4-*b*]indole (9a). Compound **8a** (30 mg, 0.11 mmol) was combined with TPP in 2 mL of CH_2Cl_2 and photooxygenated at 0 °C for 40 min. ^1H NMR of the crude reaction mixture indicated only **9a** was present. An analytical sample of **9a** was obtained by TLC (acetone:CH_2Cl_2:petroleum ether = 0.2:2:4): ^1H NMR (acetone-d_6) δ 7.94 (d, 2 H, J = 7.27 Hz), 7.66–7.59 (m, 2 H), 7.49 (t, 2 H, J = 7.57 Hz), 7.28 (m, 2 H, J = 7.48 Hz), 7.05 (td, 1 H, J = 7.51, 0.59 Hz), 6.34 (q, 1 H, J = 2.60 Hz), 5.94 (q, 1 H, J = 2.55 Hz), 5.05 (dt, ABX_2, 1 H, J_{AB} = 17.36 Hz, J_X = 2.80 Hz), 4.68 (dt, ABX_2, 1 H, J_{AB} = 17.35 Hz, J_X = 2.47 Hz); COSY was performed to find the couplings; ^{13}C NMR (acetone-d_6) δ 142.73 (s), 137.12 (s), 135.12 (d), 133.99 (s), 130.85 (d), 130.37 (d), 128.86 (d), 127.47 (s), 125.80 (d), 122.32 (d), 118.51 (d), 115.77 (d), 92.41 (d), 71.97 (t); IR (NaCl, $CDCl_3$) cm^{-1} 3000 (w), 1460 (m), 1365 (s), 1172 (s), 1079 (m), 752 (m), 721 (m); MS m/z 315 (M, 100), 286 (100); HRMS calcd for $C_{16}H_{13}NSO_4$ 315.0566, obsd 315.0565.

9,9a-Dihydro-4-methyl-9-(phenylsulfonyl)-3*H*-1,2-dioxino[3,4-*b*]indole (9b). Compound **8b** (29 mg, 0.1 mmol) was combined with methylene blue in 0.5 mL of acetone-d_6 in a 5-mm NMR tube. Photooxygenation was carried out at −78 °C for 1.0 h. ^1H NMR indicated 85% **9b** and 15% ketone **10b**. Endoperoxide **9b** was purified by TLC (acetone:CH_2Cl_2:petroleum ether = 0.3:2:4): ^1H NMR (acetone-d_6) δ 7.97 (d, 2 H, J = 7.35 Hz), 7.70 (t, 2 H, J = 7.39 Hz), 7.61 (t, 2 H, J = 7.58 Hz), 7.47 (d, 1 H, J = 7.53 Hz), 7.29 (t, 1 H, J = 7.37 Hz), 7.11 (t, 1 H, J = 7.53 Hz), 6.30 (sextet, 1 H, J = 2.31 Hz), 4.74 (dq, ABX_3, 1 H, J_{AB} = 17.7 Hz, J_X = 1.42 Hz), 4.67 (dq, ABX_3, 1 H, J_{AB} = 17.7 Hz, J_X = 1.30 Hz), 1.90 (q, 3 H, J = 1.40 Hz); ^{13}C NMR (acetone-d_6) δ 142.49 (s), 136.86 (s), 134.76 (d), 130.00 (d), 129.54 (d), 128.62 (d), 127.88 (s), 127.54 (s), 126.58 (s), 125.17 (d), 124.36 (d), 115.26 (d), 92.38 (d), 74.46 (t), 14.02 (q); IR (NaCl, $CDCl_3$) cm^{-1} 3180 (w), 2960 (w), 1449 (m), 1365 (s), 1174 (s), 958 (m), 815 (w), 754 (m), 718 (m); FAB MS m/z 330 (M, 45), 297 (100), 284 (45).

***trans*-9,9a-Dihydro-3-methoxy-9-(phenylsulfonyl)-3*H*-1,2-dioxino[3,4-*b*]indole (9c).** Compound **8c** (31 mg, 0.1 mmol) was combined with TPP in 0.5 mL of $CDCl_3$ in a 5-mm NMR tube and photooxygenated at −5 °C for 30 min. ^1H NMR showed 95% **9c** and 5% rearranged hydroxyindoline **11**. After TLC, **9c**

was completely converted to 11: ^{1}H NMR ($CDCl_3$) for **9c** δ 7.92 (d, 2 H, J = 7.55 Hz), 7.69 (d, 1 H, J = 8.13 Hz), 7.59 (t, 1 H, J = 7.37 Hz), 7.48 (t, 2 H, J = 7.74 Hz), 7.35 (d, 1 H, J = 7.59 Hz), 7.34 (t, 1 H, J = 8.00 Hz), 7.08 (t, 1 H, J = 7.52 Hz), 6.25 (t, 1 H, J = 2.16 Hz), 5.87 (t, 1 H, J = 2.35 Hz), 5.79 (t, 1 H, J = 2.12 Hz), 3.58 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.29 (s), 138.95 (s), 136.35 (s), 133.95 (d), 131.27 (d), 129.24 (d), 127.79 (d), 124.89 (d), 124.78 (s), 121.81 (d), 115.92 (d), 115.14 (d), 101.43 (d), 91.14 (d), 57.02 (q).

11: mp 118–120 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (dt, 2 H, J = 7.42, 1.54 Hz), 7.55 (tt, 1 H, J = 7.43, 1.22 Hz), 7.51–7.43 (m, 4 H), 7.37 (td, 1 H, J = 7.56, 1.22 Hz), 7.03 (td, 1 H, J = 7.53, 0.88 Hz), 6.74 (dd, 1 H, J = 3.44, 1.82 Hz), 6.30 (d, 1 H, J = 1.80 Hz), 4.72 (dd, 1 H, J = 3.40, 1.48 Hz), 3.81 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.20 (s), 153.46 (s), 144.19 (s), 139.04 (s), 133.42 (d), 133.36 (d), 129.09 (d), 127.40 (d), 124.96 (s), 123.71 (d), 122.46 (d), 114.12 (d), 110.33 (d), 84.85 (d), 52.12 (q); IR (NaCl, $CDCl_3$) cm^{-1} 3483 (s), 3100 (w), 2853 (w), 1700 (s), 1650 (s), 1600 (s), 1467 (m), 1355 (s), 1206 (m), 1170 (s), 1096 (m), 808 (m), 723 (m); MS m/z 346 (M, 7), 329 (5), 286 (12), 285 (10), 204 (55), 172 (100); HRMS calcd for $C_{17}H_{15}NSO_5$ 345.0671, obsd 345.0671.

***cis*-9,9a-Dihydro-3-methoxy-9-(phenylsulfonyl)-3*H*-1,2-dioxino[3,4-*b*]indole (9d).** Compound **8d** (22 mg, 0.07 mmol) was combined with TPP in a 5-mm NMR tube. Photooxygenation was carried at −3 °C for 40 min. ^{1}H NMR showed that only (>98%) **9d** was present: ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 2 H, J = 7.43 Hz), 7.60 (t, 2 H, J = 7.80 Hz), 7.50 (t, 2 H, J = 7.70 Hz), 7.32 (d, 1 H, J = 7.82 Hz), 7.27 (t, 1 H, J = 7.68 Hz), 7.07 (t, 1 H, J = 7.51 Hz), 6.29 (q, 1 H, J = 2.18 Hz), 5.82 (t, 1 H, J = 2.21 Hz), 5.34 (t, 1 H, J = 2.20 Hz), 3.57 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 143.12 (s), 138.60 (s), 136.80 (s), 133.90 (d), 131.15 (d), 129.26 (d), 127.83 (d), 125.05 (d), 124.71 (s), 121.94 (d), 114.97 (d), 114.19 (d), 99.39 (d), 90.83 (d), 56.18 (q); IR (NaCl, $CDCl_3$) cm^{-1} 3110 (w), 2885 (w), 1462 (m), 1367 (s), 1175 (s), 1079 (m), 950 (w), 914 (w), 859 (w), 722 (m).

Endoperoxide **9d**, on standing at room temperature for 4 h, gave 11% rearrangement to hydroxyindoline **11**. Treatment of **9d** with SiO_2 or Et_3N completely converted **9d** to **11**.

Photooxygenation of 12. Compound **12**[38] (30 mg, 0.085 mmol) was combined with 0.5 mL of $CDCl_3$ and TPP in a 5-mm NMR tube. Photooxygenation was carried out at −2 °C, monitored by ^{1}H NMR. Complete conversion of **12** required 6 h, and the ratio of **13** to **14** at this stage was 4:3. Endoperoxide **13** was identified by ^{1}H NMR: ^{1}H NMR ($CDCl_3$) δ 7.89 (d, 2 H, J = 7.50 Hz), 7.58 (t, 2 H, J = 7.60 Hz), 7.45 (m, 2 H), 7.31 (d, 1 H, J = 7.39 Hz), 7.27 (t, 1 H, J = 7.52 Hz), 7.03 (t, 1 H, J = 7.44 Hz), 6.31 (t, 1 H, J = 2.31 Hz), 6.12 (t, 1 H, J = 2.60 Hz), 5.19 (t, 1 H, J = 2.42 Hz), 4.22 (q, 2 H, J = 7.08 Hz), 1.27 (t, 3 H, J = 7.08 Hz).

The reaction mixture was left overnight to complete the rearrangement of **13** to **14**. Compound **14** was isolated by precipitation induced by adding a few drops of ether: ^{1}H NMR ($CDCl_3$) δ 8.01 (d, 2 H, J = 7.57 Hz), 7.59 (t, 2 H, J = 7.75 Hz), 7.54 (d, 1 H, J = 7.20 Hz), 7.52–7.53 (m, 3 H), 7.41 (d, 1 H, J = 1.61 Hz), 7.08 (t, 1 H, J = 7.14 Hz), 6.69 (dd, 1 H, J = 3.73, 1.61 Hz), 4.52 (d, 1 H, J = 3.74 Hz), 4.38 (q, 2 H, J = 7.12 Hz), 1.41 (t, 3 H, J = 7.12 Hz); ^{13}C NMR ($CDCl_3$) δ 182.09 (s), 161.40 (s), 157.83 (s), 145.77 (s), 138.88 (s), 135.33 (d), 133.56 (d), 129.19 (d), 127.44 (d), 124.81 (s), 123.97 (d), 123.46 (d), 114.15 (d), 112.06 (d), 82.56 (d), 62.92 (t), 14.01 (q); IR (NaCl, $CDCl_3$) cm^{-1} 3479 (m), 1731 (s), 1683 (m), 1596 (s), 1465 (m), 1380 (m), 1169 (s), 1079 (s), 749 (m); MS m/z 387 (M, 26), 314 (30), 286 (56), 172 (17), 140 (60), 77 (100); HRMS calcd for $C_{19}H_{17}NSO_6$ 387.0777, obsd 387.0777.

trans*-9,9a-Dihydro-3-methoxy-4-methyl-9-(phenylsulfonyl)-3*H*-1,2-dioxino[3,4-*b*]indole (16).** Compound **15-*Z (60 mg, 0.18 mmol) was combined with 5 mg of P–RB in 2 mL of CH_2Cl_2. Photooxygenation was carried at −78 °C for 40 min. The P–RB was filtered. By ^{1}H NMR, the filtrate contained only **16**. A single crystal of **16** was grown from 1:1 CH_2Cl_2/hexane, mp 100–102 °C: ^{1}H NMR (CD_2Cl_2, 0 °C) δ 7.89 (d, 2 H, J = 8.38 Hz), 7.72 (d, 1 H, J = 8.20 Hz), 7.62 (t, 1 H, J = 7.46 Hz), 7.49 (t, 2 H, J = 7.49 Hz) 7.40 (d, 1 H, J = 7.51 Hz), 7.34 (t, 1 H, J = 8.53 Hz), 7.13 (t, 1 H, J = 7.38 Hz), 6.19 (quintet, 1 H, J = 1.86 Hz), 5.53 (q, 1 H, J = 1.0 Hz), 3.56 (s, 3 H),1.92 (dd, 3 H, J = 1.86, 0.88 Hz); ^{13}C NMR (CD_2Cl_2, 0 °C) δ 142.13 (s), 135.98 (s), 134.45 (d), 131.33 (s), 130.37 (d), 129.63 (d), 128.22 (d), 126.62 (s), 126.13 (s), 124.89 (d), 124.52 (d), 115.06 (d), 104.30 (d), 91.77 (d), 57.17 (q), 13.82 (q); IR (CD_2Cl_2, NaCl) cm^{-1} 2944 (w), 1600 (w), 1459 (s), 1369 (s), 1174 (s), 1127 (s), 1081 (m), 956 (m); MS m/z 359 (M, 63), 327 (15), 300 (10), 218 (40), 186 (100), 158 (47), 130 (66), 77 (56); HRMS calcd for $C_{18}H_{17}NSO_5$ 359.0828, obsd 359.0835.

Treatment of **16** with SiO_2 or Et_3N gave compound **19**, which was isolated by TLC (petroleum ether:CH_2Cl_2:acetone = 4:2:0.5): ^{1}H NMR ($CDCl_3$) δ 8.00 (d, 2 H, J = 7.52 Hz), 7.60 (d, 1 H, J = 7.85 Hz), 7.54 (t, 1 H, J = 7.65 Hz), 7.49–7.46 (m, 3 H), 7.31 (t, 1 H, J = 8.40 Hz), 7.06 (td, 1 H, J = 7.84, 1.05 Hz), 6.68 (d, 1 H, J = 3.38 Hz), 4.45 (d, 1 H, J = 3.39 Hz), 3.86 (s, 3 H), 2.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.98 (s), 145.38 (s), 144.07 (s), 139.20 (s), 133.27 (d), 131.51 (d), 129.04 (d), 127.51 (d), 127.27 (d), 126.20 (s), 124.13 (s), 123.43 (d), 113.73 (d), 85.27 (d), 52.55 (q), 16.16 (q); IR (NaCl, $CDCl_3$) cm^{-1} 3487 (br, s), 2952 (w), 1708 (s), 1606 (m), 1462 (s), 1360 (s), 1256 (s), 1166 (s), 1150 (m), 723 (m); MS m/z 360 (M + 1, 11), 359 (M, 37), 342 (22), 341 (65), 328 (11), 327 (34), 300 (100), 218 (38), 200 (40), 186 (81); HRMS calcd for $C_{18}H_{17}NSO_5$ 359.0828, obsd 359.0827.

Photoxygenation of 15-*E*. Compound **15-*E*** (0.12 g, 0.37 mmol) was combined with 5 mg of P–RB in 5 mL of CH_2Cl_2. Photooxygenation was carried out at −78 °C for 20 min and the P–RB filtered. The filtrate was condensed and isolated by TLC (petroleum ether:CH_2Cl_2:acetone = 4:2:0.5). The first fraction was isomeric **15-*Z*** (15 mg, 10%). The second fraction was allylic hydroperoxide **17** (102 mg, 80%): ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1 H, br), 8.00 (d, 1 H, J = 5.64 Hz), 7.91 (d, 2 H, J = 6.00 Hz), 7.80 (s, 1 H), 7.72 (d, 1 H, J = 5.77 Hz), 7.52 (t, 1 H, J = 5.56 Hz), 7.44 (t, 2 H, J = 5.92 Hz), 7.34 (t, 1 H, J = 5.52 Hz), 7.27 (t, 1 H, J = 5.48 Hz), 5.81 (d, 1 H, J = 0.68 Hz), 5.80 (s, 1 H), 5.44 (s, 1 H), 3.58 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.02 (s), 135.06 (s), 134.50 (s), 133.90 (d), 129.31 (d), 128.46 (s), 126.85 (d), 124.91 (d), 124.62 (d), 123.65 (d), 120.64 (d), 118.90 (s), 118.85 (t), 113.69 (d), 108.00 (d), 56.12 (q); IR (NaCl, $CDCl_3$) cm^{-1} 3438 (br, s), 1448 (s), 1371 (s), 1173 (s), 1081 (m), 963 (m), 752 (m); MS m/z 359 (M, 3), 343 (8), 342 (19), 341 (56), 311 (100), 282 (30), 200 (55); HRMS calcd for $C_{18}H_{17}NSO_5$ 359.0828, obsd 359.0827.

Photooxygenation of Allylic Hydroperoxide 17. Compound **17** (40 mg, 0.11 mmol) was combined with P–RB in 0.5 mL of $CDCl_3$. Photooxygenation was carried out at 0 °C, and the process was monitored with ^{1}H NMR. Complete conversion of **17** required 14 h irradiation. Endoperoxide **18** (14 mg, 46%) was isolated by TLC (petroleum ether:CH_2Cl_2:acetone = 4:2:0.4): mp 70–72 dec; ^{1}H NMR ($CDCl_3$) δ 8.17 (d, 1 H, J = 0.8 Hz), 7.92 (dd, 2 H, J_1 = 8.43 Hz, J_2 = 1.32 Hz), 7.74 (d, 1 H, J = 8.23 Hz), 7.60 (tt, 1 H, J = 7.52, 1.12 Hz), 7.49 (t, 2 H, J = 8.49 Hz), 7.43 (d, 1 H, J = 6.85 Hz), 7.34 (td, 1 H, J = 7.71, 1.27 Hz), 7.10 (td, 1 H, J = 7.62, 0.94 Hz), 6.31 (septet, 1 H, J = 1.20 Hz), 5.34 (s, 1 H), 5.03 (dd, ABX, 1 H, J_{AB} = 17.2 Hz, J_X = 3.17 Hz), 4.74 (dq, ABX_3, 1 H, J_{AB} = 17.2 Hz, J_X = 1.11 Hz), 3.53 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.88 (s), 136.17 (s), 134.05 (d), 132.48 (s), 130.81 (d), 129.29 (d), 128.42 (s), 128.02 (d), 125.81 (s), 124.85 (d), 124.80 (d), 114.89 (d), 104.12 (d), 91.67 (d), 70.71 (t), 57.12 (q); IR (NaCl, $CDCl_3$) cm^{-1} 3439 (br, s), 2919 (w), 1602 (m), 1446 (s), 1367 (s), 1173 (s), 1082 (s), 950 (m), 900 (m), 757 (m), 726 (s); MS m/z 391 (M, 22), 359 (10), 343 (10), 285 (35), 284 (100), 257 (30); HRMS calcd for $C_{18}H_{17}NSO_7$ 391.0726, obsd 391.0726.

Photooxygenation of 15-*E* with Trimethyl Phosphite. Compound **15-*E*** (32 mg, 0.1 mmol) was dissolved in a 10-mm NMR tube with TPP and 1.0 mL of CH_2Cl_2. Trimethyl phosphite (17.2 μL, 0.15 mmol) was injected into the tube and photooxygenated at −90 °C for 1.5 h. The resulting reaction mixture was condensed and isolated by TLC (petroleum ether:CH_2Cl_2:acetone = 4:2:0.5) to give aldehyde **21** (21 mg, 70%), mp 109–110 °C. ^{1}H NMR ($CDCl_3$) δ 9.76 (s, 1 H), 8.19 (s, 1 H), 8.04 (dd, 1 H, J = 9.03, 0.91 Hz), 7.94 (dt, 2 H, J = 8.92, 1.98 Hz), 7.67 (d, 1 H, J = 7.53 Hz), 7.53 (t, 1 H, J = 8.80 Hz), 7.46 (t, 2 H, J = 8.56 Hz), 7.34 (td, 1 H, J = 7.89, 1.02 Hz), 7.29 (t, 1 H, J = 7.80 Hz), 6.93 (s, 1 H), 6.33 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 192.97 (d), 140.49 (s), 138.00 (s), 134.93 (t), 134.78 (s), 133.99 (d), 129.36 (d), 128.78 (s), 126.93 (d), 126.82 (d), 125.04 (d), 123.74 (d), 120.51 (d), 114.09 (s), 113.78 (d); IR (KBr pellet) cm^{-1} 3171 (m), 3100 (w), 2839 (w), 2731 (m), 1702 (s), 1620 (w), 1449 (s), 1368 (s), 1183 (s), 968 (m), 751 (m); MS m/z 312 (M + 1, 19), 311 (M, 100), 282 (17), 170 (32), 142 (73), 115 (60), 77 (61); HRMS calcd for $C_{17}H_{13}NSO_3$ 311.0617, obsd 311.0617.

Competition with $^1O_2$ between 4-*E* and 4-*Z*. Compounds 4-*E* (10 mg) and 4-*Z* (12.5 mg) were combined in a 5-mm NMR tube with TPP and 0.5 mL of CD_2Cl_2. Photooxygenation was carried out at −78 °C for 5 min, and the resulting reaction mixture was examined by ^1H NMR at −45 °C. At this stage, conversion of 4-*Z* is 50% and conversion of 4-*E* is 15.5%. k_Z/k_E was calculated to be 4.1 with integration at 6.67 (d) for 5, 6.62 (d) for 6, 5.95 (d) for 4-*E*, and 6.61 (d) ppm for 4-*Z*, respectively, using the integrated competition kinetic equation.[72]

Competitions with $^1O_2$ between 8c and 8d and between 4-*E* and 8d were done similarly; k_Z/k_E was 5.2 for 8; 4-*E* reacted with $^1O_2$ 5 times faster than 8d.

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Supplementary Material Available: ^1H NMR spectra for all new compounds (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Dehydroamino Acid Derivatives from D-Arabinose and L-Serine: Synthesis of Models for the Azinomycin Antitumor Antibiotics[1]

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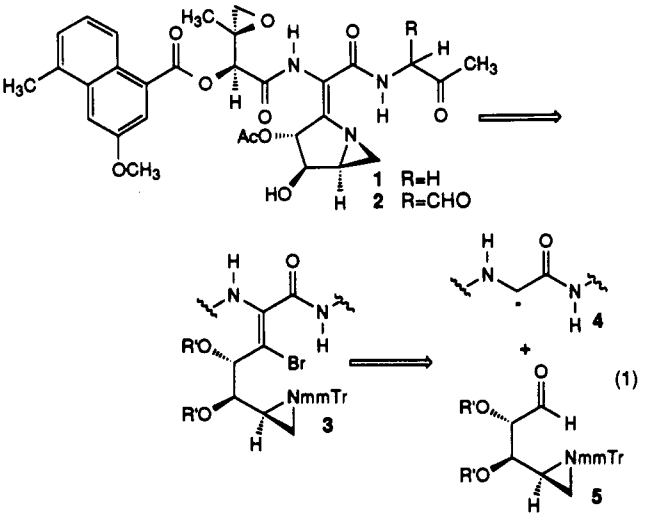
Synthesis of aldehydes 17 from D-arabinose and 31 from L-serine provided key precursors for the generation of highly functionalized dehydroamino acid derivatives upon condensation with glycyl phosphonates. Subsequent bromination and intramolecular addition/elimination afforded the azabicyclo[3.1.0]hex-2-ylidene ring system postulated to exist in the azinomycin antitumor antibiotics.

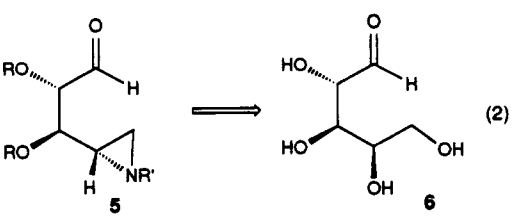
Introduction

The antitumor antibiotics azinomycin A (1) and B (2) were recently isolated from the fermentation broth of *Streptomyces griseofuscus*.[2] An in vitro assay has established that azinomycin B induces interstrand cross-links in duplexed DNA between G and purine residues two base-pairs removed.[3] Azinomycin B also monoalkylates single-stranded DNA and duplex DNA exclusively at G residues. Piperidine treatment of monoalkylation intermediates results in depurination and strand scission as has been observed for adducts of DNA with synthetic aziridine reagents.[4] We have postulated that the bicyclic and vinylic aziridine proposed to exist in the natural products is responsible for the monoalkylation of G residues. In the case of duplex DNA, a second alkylation of a purine residue two bases removed in the 5′ direction results in cross-link formation. In the context of our work on the mechanism of action of the azinomycins, we have been engaged in the total synthesis of these compounds and of selected analogs. We recently reported in communication form the syntheses of 1-azabicyclo[3.1.0]hex-2-ylidene dehydroamino acid derivatives **36Z**, **41Z**, and **41E**.[5,6] These are the first synthetic compounds to contain the intact vinylic bicyclic aziridine moiety proposed for the azinomycin antibiotics. These compounds were obtained via Horner–Emmons condensation of a glycine phosphonate with aldehyde 17.[6] Described herein are two syntheses of aldehydes of the type represented by structure **5**,[7] starting from D-arabinose and L-serine. Full details on the conversion of the dehydroamino acid derivatives to (*Z*)- and (*E*)-azabicyclo[3.1.0]hex-2-ylidenes are also provided.



Results and Discussion

Our retrosynthetic strategy for the azinomycin skeleton is outlined in eq 1. Disconnection of the labile 1-azabicyclo-[3.1.0]hex-2-ylidene ring system and separation of the upper and lower halves generates key intermediate target compounds 4 and 5. Aldehyde 5 is linear, bears heteroatom substitution on each of its five carbons, and contains three contiguous stereocenters. These features suggested that it could be synthesized through transformation of an appropriate sugar. The relative configuration of D-arabinose (6) matched that assigned to the natural product with the exception of C-4, which could be generated via a Walden inversion involving a nitrogen nucleophile (eq 2).



D-Arabinose was converted to its 1,1-bis(ethylthio)-4,5-isopropylidene derivative 7 as previously described[8] (Scheme I). Treatment of 7 with *p*-methoxybenzyl chloride and NaH in DMF resulted in formation of bis-protected product 8. The discovery that a mesyl or tosyl

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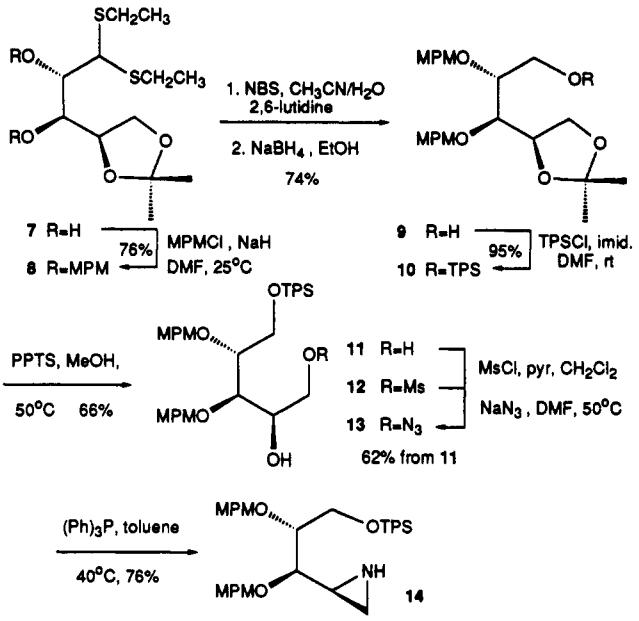
Scheme I

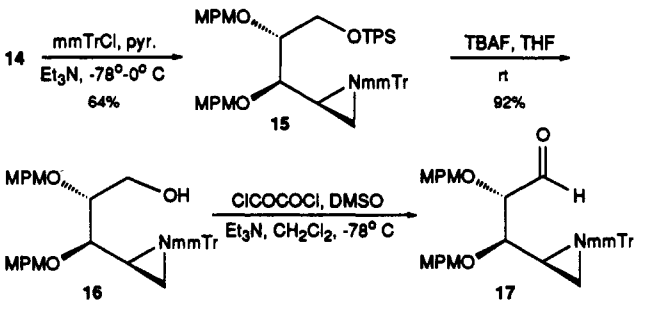


group in the C-4 or C-5 position was incompatible with a C-1 thioacetal derivative convinced us that, before activation of either of these oxygens for nucleophilic displacement, an alternative protecting group at C-1 would have to be introduced. Thus, NBS deprotection[9] of **8** followed immediately by reduction of the crude aldehyde with $NaBH_4$ in EtOH led to alcohol **9**. Silylation under standard conditions afforded **10** followed by removal of the isopropylidene protecting group with mild acid to generate diol **11**. Azide **13** was obtained via selective mesylation at C-5 and subsequent treatment with sodium azide. Transformation to the aziridine **14** was effected by concomitant reduction and cyclization via the aza-ylide intermediate under Staudinger conditions.[10]

Consideration of the synthetic strategy at this point required a judicious choice of a protecting group for the aziridine in **14**. Initial studies with carboethoxy and FMOC protecting groups were discouraging, since the resulting carbamate aziridines spontaneously underwent intramolecular aziridine opening to form tetrahydrofuran products upon fluoride deprotection of the primary alcohol. A report by Nakajima[11] on the stability of an aziridine-2-carboxylate to trifluoroacetic acid (TFA)-promoted *N*-trityl deprotection prompted us to prepare the monomethoxytrityl protected aziridino aldehyde **17** from **14** (Scheme II). In contrast to the carbamate derivatives, alcohol **16** proved to be sufficiently stable when generated through deprotection of **15** with TBAF in THF followed by chromatography. Prompt oxidation to aldehyde **17** prevented any undesirable cyclization products. Although this aldehyde could not be chromatographed on silica gel, ^1H NMR analysis of the crude reaction mixture indicated that the product was of high purity.

Subsequent experiments using **17** convinced us that the monomethoxytrityl-protected aziridine was remarkably stable to a variety of conditions (vide infra). However, we sought a synthesis of aldehydes of type **5** which would

Scheme II



provide greater latitude in the selection of blocking groups for the C-2 and C-3 hydroxyls and which specifically would allow for silyl protecting groups in these positions. These factors led us to the synthesis of **31** from L-serine (Scheme III). Serine methyl ester (**18**) was converted to alcohol **21** without purification of intermediates in excellent overall yield. This material proved to be stable to freezer storage (>6 months) without racemization. Oxidation and homologation provided ester **23** which was subsequently reduced and blocked with dimethoxytrityl chloride, affording **25**. Sharpless asymmetric hydroxylation[12] provided an inseparable mixture of diastereomers **26** and **27** in a 4.1:1 ratio, respectively.[13] Subsequent protection with TESCl (or TBSOTf[14]) afforded **28** containing a trace of the minor diastereomer. Acid treatment followed by selective reprotection afforded alcohol **30** as a single diastereomer which was oxidized to **31** using Swern conditions. Like **17**, aldehyde **31** was unstable to chromatography, but could be used as crude reaction mixture in subsequent condensation reactions.

Our first attempts at condensation of **17** with a glycine anion equivalent were via the acidic Erlenmeyer reaction.[15] Before attempting this reaction, we confirmed the stability of the (monomethoxytrityl)aziridine to the reaction conditions by recovering **15** in high yield following treatment with $Pb(OAc)_4/Ac_2O$ in THF at 60 °C for approximately 12 h.[16] However, condensation of **17** with hippuric acid using the Erlenmeyer conditions followed by addition of primary amines provided only low yields of dehydroamino acid (DHAA) products.

Instead of pursuing variations on the Erlenmeyer synthesis, we turned instead to the more versatile glycine phosphonate approach for a DHAA synthesis. Both α-phosphono esters and phosphono amides have demonstrated usefulness in natural product synthesis.[17] Attempted condensation of ethyl *N*-benzoyl-α-(diethylphosphono)glycinate (**32**)[18] with aldehyde **17** (Scheme IV) using t-BuOK in CH_2Cl_2 at low temperature led to extensive decomposition of **17**.[19] Use of LDA in THF, however, provided good yields of the desired dehydroamino ester products **33E** and **33Z**. Ester **33Z** could be suc-

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