have also shown the use of ^3H–^1H correlation and J-resolved spectroscopy experiments to aid in labelling studies and in spectral assignment. It should be noted that neither change of solvent nor progressive addition of paramagnetic shift reagent (Eu(fod)$_3$) resolved the 4- and 5-protons in the ^1H NMR spectra—these chemical shifts were readily obtained from the ^3H NMR spectra.

In the course of preparing labeled compounds for these studies, two other interesting phenomena were observed. The first was an isotope effect in the oxidation of [1-^3H]benzyl alcohol to benzaldehyde; the analogous deuterium isotope effect has been reported previously.[16] Secondly, the proposed preparation of the 2-^3H compound by decomposition of cinnamylidenemalonic acid in the presence of HTO and pyridine yielded tritium in both the 2- *and* 4-positions. This reaction is believed to have two mechanisms under the conditions used in this preparation.[17] The first is decarboxylation of the diacid to yield label in the 2-position. The second has been proposed as involving formation of a lactone, exchange of the allylic position (4-position in the product compound), followed by a concerted ring opening and decarboxylation step, to yield the dienoic acid.

By way of clarifying the chemical shifts and coupling relations in the 2*E*,4*E* isomer of 5-phenylpenta-2,4-dienoic acid we have illustrated the usefulness of tritium and deuterium labeling in resolving NMR anomalies.

Experimental Section

NMR. Proton NMR spectra were obtained at both 90 and 300 MHz. The 90-MHz spectra were obtained on a Bruker WH-90 spectrometer, in deuteriated solvent, with tetramethylsilane as internal standard. The spectra were acquired at 25 °C, with pulse widths of 1.5–3 μs, recycle delays of 1.6–3.4 s, and 8K data points over a sweep width of 1200 Hz. Tritium NMR spectra were recorded at 96 MHz on the same spectrometer under the same conditions, and triton shifts were measured from a ghost reference derived from the ^1H signal of the internal Me_4Si.[18]

The 300-MHz proton NMR spectra were obtained on an IBM Instruments AF-300 spectrometer, at 25 °C, using 8K data points, a sweep width of 3 kHz, and a pulse width of 6 μs. The data for the phase-sensitive COSY, with sampling of 400 t_1 values, were collected and processed with standard Bruker DISNMR software.

The four-spin spectral simulation was calculated by the use of the PANIC program, which is also standard Bruker software for the AF series of spectrometer.

Syntheses: 5-Phenyl[2,4-$^3H_2$]penta-2,4-dienoic Acid. Cinnamylidenemalonic acid (300 mg), tritiated water (10 μL, 1850 GBq mL^{-1}), and pyridine (4 mL) were heated together under reflux for 8 h. Water (10 mL) was then added, the solution was acidified (3 N HCl), and the precipitate was recrystallized from benzene. The dienoic acid (110 mg; 6.66 GBq mmol^{-1}), mp 164–165 °C, had ^3H NMR [$(CD_3)_2SO$] δ 6.08 (s, 2-^3H) and 7.13 (s, 4-^3H).[17]

5-Phenyl[5-^3H]penta-2,4-dienoic Acid. This compound was prepared by the Reformatskii reaction of [1-^3H]benzaldehyde (95 mg) with ethyl γ-bromocrotonate (112 mg), followed by dehydration and alkaline hydrolysis. The [1-^3H]benzaldehyde (1.63 GBq mmol^{-1}) was prepared by oxidation of [1-^3H]benzyl alcohol (1.92 GBq mmol^{-1}) by CrO_3 in pyridine. The product of the Reformatskii reaction was dissolved in benzene and dehydration was effected by addition of a trace of *p*-toluenesulfonic acid and heating. Hydrolysis of the resultant ethyl ester was achieved by addition of a saturated solution of KOH in ethanol. The yield was 30 mg of material with specific activity 1.63 GBq mmol^{-1} and mp 165 °C. NMR analysis with broad-band proton decoupling yielded ^3H NMR [$CDCl_3$] δ 6.96 (s) and proton-coupled δ 6.90 (d, $J_{4^1H\text{-}5^3H}$ = 15.3 Hz).

5-Phenyl[$^2H_5$]penta-2,4-dienoic Acid. [$^2H_5$]Benzaldehyde (1.0 g) and ethyl γ-bromocrotonate (1.2 g) were used as the starting materials in the Reformatskii reaction. The product was isolated and purified as above, with a yield of 300 mg, mp 164–165 °C, M^+ 179. The ^1H NMR spectrum of the product is shown in Figure 1C, and the shifts and coupling constants are in Table I.

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syn- and *anti*-Dioxasesquinorbornenes. Singlet Oxidation of Exocyclic *s-cis*-1,3-Butadienes

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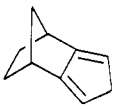
In the early 1980s a large amount of data was collected which demonstrated that isodicyclopentadiene (**1**) un-



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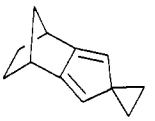
dergoes 4 + 2 cycloaddition preferentially on the bottom face.[1] Orbital tilting,[2] which results in severe closed shell repulsion when top approach is attempted, and a torsional/steric[3] argument were presented to explain this novel behavior. In 1980 Paquette and co-workers[4] reported that only moderate bottom selectivity was observed in the reaction of **1** with singlet oxygen. Endoperoxides, however, were not directly observed in the reactions of **1** and several of its alkylated derivatives[5] and the π-facial selectivity was inferred from examination of the decomposition products.

We report here that the endoperoxides from reactions of **1** and its spirocyclopropyl derivative **2** can be directly



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observed and the π-facial selectivity directly determined. In addition, we report the rates of singlet oxygen addition to both **1** and **2** and several exocyclic *s-cis*-1,3-butadienes.

The addition of singlet oxygen to **1** was accomplished by irradiation of an acetone-d_6 solution of **1** and rose bengal at −78 °C through at 0.5% potassium dichromate filter. The extent of reaction was monitored by ^1H and ^{13}C NMR at −80 °C. Upon completion of the reaction the proton-

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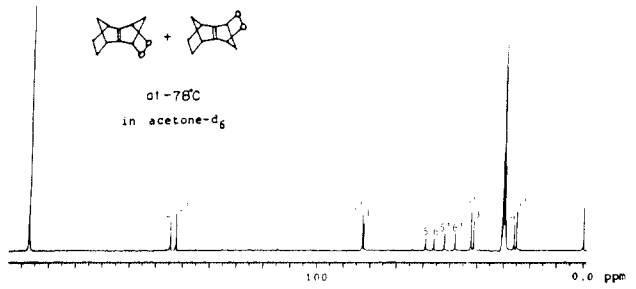
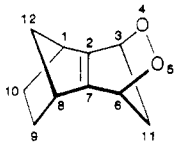


Figure 1. ^{13}C NMR of dioxasesquinorbornenes **3** and **4** at −78 °C.

decoupled ^{13}C NMR exhibited 12 peaks (Figure 1). At −25 °C one set of six peaks (1–6) disappeared more rapidly than the other set (1′–6′), confirming formation of two different products. We suggest that peaks 1–6 belong to endoperoxide **3** and peaks 1′–6′ to endoperoxide **4**. This



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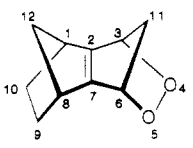

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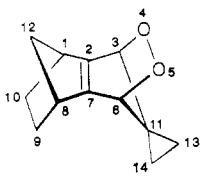
assignment was based on the previously observed[6] dramatic shielding of the methylene bridges in *syn*-sesquinorbornene derivatives in comparison to their anti isomers. The ^{13}C chemical shifts (Table I). were assigned with the aid of the coupled spectrum and an integrated spectrum collected under conditions that allowed complete relaxation and neglect of nuclear Overhauser enhancement. The more rapid disappearance of *anti*-dioxasesquinorbornene **3** is consistent with MM2 calculations, which indicate that *syn*-sesquinorbornene is several kcal/mol more stable than *anti*-sesquinorbornene.[7] This stability order (**4** > **3**) is reversed from that deduced from examination of the MINDO/3 heats of formation of **3** and **4**.[4] However, MNDO also fails to predict the pyramidalization of *syn*-sesquinorbornene.

The spirocyclopropyl derivative **2** exhibited reactivity very similar to the parent **1** and produced only the endoperoxides **5** and **6**. The ^{13}C data for these compounds are



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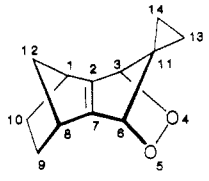
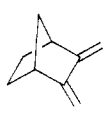


6

also presented in Table I. The π-facial selectivity for bottom attack, however, was slightly greater for **2** (**6**/**5** = 1.7) than for the parent **1** (**4**/**3** = 1.2).

The rates of reaction of singlet oxygen with **1** and **2** and exocyclic *s-cis*-1,3-butadienes[8] **7**–**9** are shown in Table II



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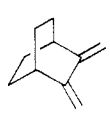

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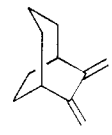

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Table I. ^{13}C NMR Spectral Data for Dioxasesquinorbornenes 3–6

		δ (relative to Me_4Si)[b]			
peak[a]	carbon	**3**	**4**	**5**	**6**
3	1, 8	41.3	42.4	41.9	42.8
2	2, 4	154.4	152.7	156.2	154.2
1	3, 6	82.6	83.1	85.8	87.0
4	9, 10	26.2	24.4	25.9	25.5
5	11	59.3	52.3	58.3	48.6
6	12	56.2	48.3	53.0	48.0
	13[c]			8.24	10.8
	14[c]			5.25	3.56

[a] Peak number in Figure 1. [b] In acetone-d_6 at −78 °C. [c] Could be switched.

Table II. Rates of Reaction of *s-cis*-1,3-Butadienes with Singlet Oxygen, TCNE,[a] and MA[b]

diene	$r_{1,4}$ (Å)	$k(^1O_2)$ (M^{-1} s^{-1})	k(TCNE) (M^{-1} s^{-1})	k(MA) (M^{-1} s^{-1})
1	2.36	1.5×10^8		
2	2.36	1.3×10^8		
c[17]	2.36	2.3×10^7	957	0.0678
9	3.03	1.7×10^6	9.6	0.0119
8	3.08	1.7×10^6	3.08	0.00316
7	3.17	3.6×10^5	0.161	0.000173
$k_{fastest}/k_{slowest}$		416.67	5944.10	391.9

[a] Tetracyanoethylene. [b] Maleic anhydride. [c] Cyclopentadiene.

along with the 1,4-distance (r_{14})[9] in the diene, and their rates of reaction with tetracyanoethylene (TCNE) and maleic anhydride (MA).[9a] Singlet oxygen conforms to the same trend as noted previously,[9] it is more reactive with dienes with short C_1–C_4 distances indicative of a concerted reaction.[10] The selectivity ($k_{fastest}/k_{slowest}$) of singlet oxygen for these dienes, however, is much smaller than the selectivity exhibited by TCNE. Selectivity often increases with increasing reactivity of dieneophiles in 4 + 2 cycloadditions. This reversal of the normal reactivity selectivity principle[11] has been explained in terms of a FMO model.[12] The unique behavior of singlet oxygen is explicable in terms of the intervention of an exciplex intermediate.[13]

Experimental Section

Preparative gas chromatographic separations were carried out on a GOW MAC gas chromatograph utilizing a 0.25 in. by 20 ft column packed with 20% Carbowax 20M on Chromosorb W for dienes **7**–**9** and on a 0.25-in. by 4 ft column packed with 20% Carbowax 20M on Chromosorb P for diene **1** and **2**. Proton and carbon NMR spectra were obtained on a JEOL FX270 at 270 and 63.8 MHz respectively, and the chemical shifts were referenced to Me_4Si. Mass spectral data were obtained on a VG-ZAB-1F instrument. IR were obtained on a Beckman Microlab 600 spectrometer. Kinetic studies were carried out on a Cary 2300 spectrometer, a Hitachi 100-80 spectrophotometer, and a Perkin-Elmer MPF-2A spectrofluorometer.

2,3-Dimethylenebicyclo[2.2.1]heptane (7) was synthesized by the method of Butler and Snow[14] and purified by preparative

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gas chromoatography. The retention time was 50 min when the oven was set to 145 °C, the injector to 198 °C, the detector to 225 °C, and the collector to 199 °C with a Helium flow rate of 15 mL/min. **7**: ^{1}H NMR (acetone-d_6) δ 5.08 (s, 2 H), 4.77 (s, 2 H), 2.79 (br s, 2 H), 1.29–1.76 (m, 6 H); ^{13}C NMR (acetone-d_6) δ 153.2, 100.0, 46.2, 39.6, 29.3.

2,3-Dimethylenebicyclo[2.2.2]octane (8) was synthesized by the method of Butler and Snow[14] and purified by preparative gas chromatography. The retention time was 60 min when the oven was set to 130 °C, the injector to 195 °C, the detector to 220 °C, and the collector to 200 °C. **8**: ^{1}H NMR (acetone-d_6) δ 5.23 (s, 2 H), 4.69 (s, 2 H), 2.30 (br s, 2 H), 1.66 (d, J = 7.3 Hz, 4 H), 1.53 (d, J = 8.1 H, 4 H); ^{13}C NMR (acetone-d_6) δ 150.4, 103.5, 31.1, 26.8.

2,3-Dimethylenebicyclo[2.2.3]nonane (9) was synthesized by the method of Butler and Snow[14] and purified by preparative gas chromatography. The retention time was 30 min when the oven was 128 °C, the injector 189 °C, the detector 212 °C, and the collector 182 °C. **9**: ^{1}H NMR δ 5.30 (s, 2 H), 4.69 (s, 2 H), 2.60 (br s, 2 H), 1.42–1.75 (m, 8 H); ^{13}C NMR δ 150.3, 106.6, 40.9, 36.3, 26.8, 21.9.

Isodicyclopentadiene (1) was synthesized by the method of Alder[15] and purified by the method of gas chromatography. The retention time was 10.5 min when the oven was set to 125 °C and the detector to 200 °C with a He flow rate of 63 mL/min. **1**: ^{1}H NMR (acetone-d_6) δ 5.62 (br s, 2 H), 2.91–3.18 (m, 4 H), 1.25–1.86 (m, 6 H); ^{13}C NMR (acetone-d_6) δ 156.2 (s), 114.5 (d), 46.5 (t), 45.5 (t), 39.1 (d), 29.1 (t).

4′,5′,6′,7′-Tetrahydrospirocyclopropene-1,2′-4,7-methano-2*H*-indene (2) was synthesized by the method of Paquette[16] and purified by preparative gas chromatography. The retention time was 17 min when the oven was set to 144 °C, the injector to 148 °C, and the detector to 211 °C with a He flow rate of 69 mL/min. **2**: ^{1}H NMR (acetone-d_6) δ 5.32 (br s, 2 H), 3.01 (br s, 2 H), 1.88–1.30 (m, 10 H); ^{13}C NMR (acetone-d_6) δ 152.9 (s), 122.0 (d), 46.8 (t), 40.6 (s), 39.5 (d), 29.4 (t), 11.2 (t), 10.2 (t).

General Photolysis Conditions. The diene (10–30 mg) and 1.0 mg of rose bengal were mixed with 0.6–0.7 mL of acetone-d_6 in a 5-mm NMR tube and saturated with oxygen for 25 min at −78 °C while being protected from the room lights. The solution was irradiated through a 0.5% $K_2Cr_2O_7$ filter solution (1 cm pathlength, cutoff approximately 500 nm). The progress of the reaction was monitored by low-temperature NMR at −80 °C.

4,5-Dioxatricyclo[6.2.1.0^{2,7}]undec-2(7)-ene: ^{1}H NMR (acetone-d_6; −78 °C) δ 4.85 (d, J = 16.1 Hz, 1 H), 4.66 (d, J = 15.4 Hz, 1 H), 4.49 (d, J = 15.4 Hz, 1 H), 4.25 (d, J = 16.1 Hz, 1 H), 2.83 (s, 2 H), 1.00–1.64 (m, 6 H); ^{13}C NMR (acetone-d_6; −78 °C) δ 136.84, 135.24, 69.46, 67.88, 45.45, 41.63, 41.38, 25.10, 24.83; ^{1}H NMR (acetone-d_6; 25 °C) δ 4.67 (d, J = 14.3 Hz, 2 H), 4.43 (d, J = 14.3 Hz, 2 H), 2.86 (s), 1.05–1.70 (m, 6 H); ^{13}C NMR (acetone-d_6; 25 °C) δ 137.87, 70.16, 43.16, 26.41, 47.03.

4,5-Dioxatricyclo[6.2.2.0^{2,7}]dodec-2(7)-ene was isolated by flash column chromatography: ^{1}H NMR (acetone-d_6; −78 °C) δ 4.77 (d, J = 14.6 Hz, 2 H), 4.28 (d, J = 14.6 Hz, 2 H), 2.36 (s, 2 H), 1.51 (br s, 4 H), 1.21 (br s, 4 H); ^{13}C NMR (acetone-d_6; −78 °C) δ 132.14, 68.97, 28.82, 25.25, 24.86; ^{1}H NMR ($CDCl_3$; 25 °C) δ 4.59 (s, 4 H), 2.38 (s, 2 H), 1.60 (m, 4 H), 1.33 (m, 4 H); ^{13}C NMR ($CDCl_3$; 25 °C) δ 133.13 (s), 70.58 (t, J = 144 Hz), 30.24 (d, J = 136 Hz), 26.28 (t, J = 133 Hz); IR (cm^{-1}) 2934, 2859, 2812, 1349, 1000, 960, 776; high resolution mass spectrum calculated for $C_{10}H_{14}O_2$, m/e (M^+) 166.0994, found m/e (M^+) 166.0987; mp 57–59 °C.

4,5-Dioxatricyclo[6.3.2.0^{2,7}]tridec-2(7)-ene was isolated by flash column chromatography: ^{1}H NMR (acetone-d_6; −78 °C) δ 4.82 (d, J = 16.1 Hz, 1 H), 4.70 (d, J = 16.1 Hz, 1 H), 4.28 (d, J = 16.8 Hz, 1 H), 4.22 (d, J = 16.8 Hz, 1 H), 2.23 (br s, 2 H), 2.00–1.42 (m, 10 H); ^{13}C NMR (acetone-d_6; −78 °C) δ 134.42, 134.04, 71.63, 70.65, 32.59, 32.38, 30.36, 29.79, 25.66, 23.95, 23.95; ^{1}H NMR ($CDCl_3$; 25 °C) δ 4.47 (d, J = 14.3 Hz, 2 H), 4.37 (d, J = 14.3 Hz, 2 H), 2.19 (s, 2 H), 1.50–1.90 (m, 10 H); ^{13}C NMR ($CDCl_3$; 25 °C) δ 133.13 (s), 71.30 (t, J = 143 Hz), 32.49 (d, J = 125 Hz), 29.73 (t, J = 128 Hz), 25.73 (t, J = 131 Hz), 23.12 (t, J = 124 Hz); IR (cm^{-1}) 2862, 1445, 1343, 1015; high resolution mass spectrum calculated for $C_{11}H_{16}O_2$, m/e (M^+) 180.1151, found m/e (M^+) 180.1152; mp 42–44 °C.

***syn*- and *anti*-4,5-Dioxasesquinorbornenes (3 and 4)**: ^{1}H NMR (acetone-d_6; −78 °C) δ 5.47 (s, 2 H), 5.46 (s, 2 H), 3.06 (s, 2 H), 3.03 (s, 2 H), 2.26–0.92 (m, 16 H); ^{13}C NMR (acetone-d_6; −78 °C) δ 154.4 (s), 152.7 (s), 83.1 (d, J = 168 Hz), 82.6 (d, J = 166 Hz), 59.3 (t, J = 139 Hz), 56.2 (t, J = 131 Hz), 52.3 (t, J = 140 Hz), 48.3 (t, J = 131 Hz), 42.4 (d, J = 149 Hz), 41.3 (d, J = 148 Hz), 26.2 (t, J = 135 Hz), 24.4 (t, J = 135 Hz).

***syn*- and *anti*-11-Cyclopropyl-4,5-dioxasesquinorbornenes (5 and 6)**: ^{1}H NMR (acetone-d_6; −78 °C) δ 4.93 (s, 2 H), 4.87 (s, 2 H), 3.10 (br s, 4 H), 2.14–0.60 (m, 20 H); ^{13}C NMR (acetone-d_6; −78 °C) δ 156.2 (s), 154.2 (s), 87.0 (d, J = 166 Hz), 85.8 (d, J = 166 Hz), 58.3 (s), 53.0 (t, J = 137 Hz), 48.6 (s), 48.0 (t, J = 134 Hz), 42.8 (d, J = 149 Hz), 41.9 (d, J = 149 Hz), 25.9 (t, J = 138 Hz), 25.5 (t, J = 136 Hz), 10.8 (t, J = 164 Hz), 8.24 (t, J = 152 Hz), 5.25 (t, J = 160 Hz), 3.56 (t, J = 160 Hz).

Kinetics. The rates were measured by using the Young method as described previously.[13b]

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Communications

Structure of FR900452, a Novel Platelet-Activating Factor Inhibitor from a *Streptomyces*

Summary: The structure of FR900452 (1) isolated from a *Streptomyces* as a potent inhibitor of platelet-activating factor has been deduced by using chemical modifications, spectroscopic measurements, and an X-ray crystal analysis of the dihydro derivative **2**.

Sir: FR900452 (1) was recently isolated from *Streptomyces phaeofaciens* No. 7739 as a potent and specific inhibitor of platelet-activating factor (PAF), an endogeneous mediator of anaphylaxis and inflammation.[1] We now report the structural elucidation of this novel natural product as **1**. The 5-(2-oxocyclopent-3-en-1-ylidene)-2-oxopiperazinyl skeleton of **1** is unique.

FR900452 was isolated as a pale-yellow powder: $C_{22}H_{25}N_3O_3S$ (HRMS: obsd, m/z 411.1567; calcd, 411.1618. Anal. Calcd for $C_{22}H_{25}N_3O_3S$: C, 64.21; H, 6.21; N, 10.21; S, 7.79. Found: C, 63.90; H, 6.31; N, 9.80; S, 7.52); $[\alpha]^{23}_D$ +97.0° (c 0.5, $CHCl_3$); UV (MeOH) 246 nm (ε 13 600), 347 (14 500); IR ($CHCl_3$) 3350, 2900, 1670, 1610, 1595 cm^{-1}. The

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