Photooxidation of *anti*-1,2,3,4,5,6,7,8-Octahydro-1,4,5,8-dimethanonaphthalene ("Sesquinorbornene"). Specific Steric Effects in the Hydrocarbon and Its Precursors

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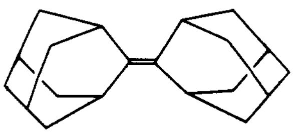
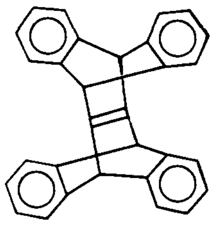
Abstract: The title compound **1** has been prepared by electrolysis of the dibasic acid **12**, whose anhydride **7** is available by a Diels–Alder-hydrogenation sequence. Neither of the syn anhydrides **6** or **8** could be hydrolyzed. X-ray crystallographic studies show that access of a nucleophile to the carbonyl groups of **6** and **8** is blocked by both ethylene bridges lying rigidly on the required approach path. Thus **2**, the syn isomer of **1**, is unavailable at present. The olefin **1**, though structurally analogous to many compounds which react with singlet oxygen, yields no peroxidic products under conditions of either thermal or photochemical singlet oxygen generation. In contrast, it reacts readily with *m*-chloroperbenzoic acid and with oxygen photosensitized by biacetyl to yield the epoxide **14**. In this oxygenation reaction **1** appears about five times as reactive as biadamantylidene. It is shown that the placement of the bridge hydrogen atoms in **1** should totally block concerted reaction with the $C{=}C$ π orbital as a whole, while still allowing bond formation at one end of the double bond. It is concluded that epoxidizing agents have the latter capability while singlet oxygen does not. Structures like **1** may have general usefulness in addition to other devices for sorting out concerted and stepwise mechanisms of attack on the double bond.

Considerable interest is attached to those specially constituted olefins which react with singlet oxygen in competition with its quenching, yet cannot undergo the usually preferred ene mode of reaction and which hence yield dioxetanes. Biadamantylidene (A) is a familiar example of this capability.


A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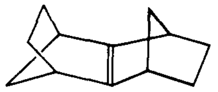
The ene reaction is here prevented by the "Bredt's rule" effect, all the α-hydrogen atoms being at bridgeheads, while the full activation of a tetrasubstituted olefin is present. A second way of flanking a double bond by bridgehead hydrogen atoms is seen in dehydrojanusene (B),[3] where the double bond lies within, instead of linking, the bicyclic systems. It has been observed[4] that dehydrojanusene is very unreactive toward singlet oxygen, though subject to other oxidations and photorearrangement in light of shorter wavelength. The present work was undertaken to prepare and study a simple example of an all-alicyclic Bredt-limited olefin, "sesquinorbornene" (1,2,3,4,5,6,7,8-octahydro-1,4,5,8-dimethanonaphthalene), of which anti (**1**) and syn (**2**) isomers are possible.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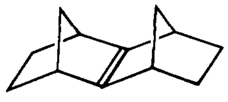
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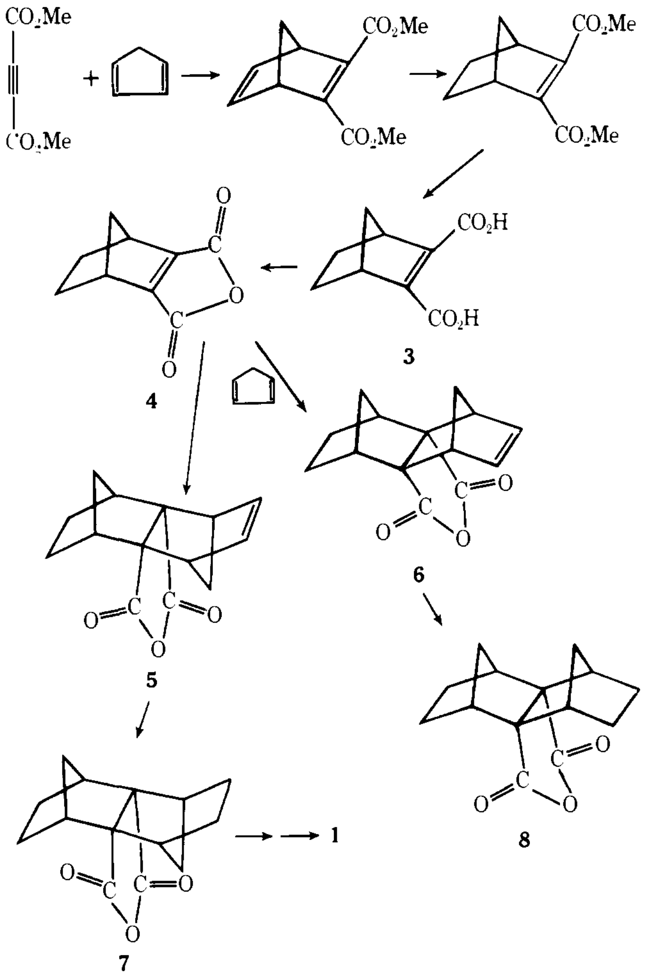
We report here the successful preparation of the anti isomer **1** and some observations on its photooxidation and on the structural and stereochemical dependence of some of the reactions in the synthetic sequence.

Scheme I



Results

The synthesis of the anhydrides **10** and **11** (Scheme II) was accomplished by Edman and Simmons[5] in 1968. We followed the modified approach of Scheme I, using norbornene-2,3-dicarboxylic anhydride **4** instead of the norbornadiene anhydride **9** of Scheme II. The Diels–Alder reaction of **4** with cyclopentadiene catalyzed by silica gel[6] led to the anti and syn anhydrides **5** and **6** in a ratio of about 3:2. This was so different from the 60:1 or 70:1 ratio of **10** and **11** found by Edman and Simmons that we repeated their reaction with the silica gel procedure to find out whether this catalyst made the difference. Our yields of **10** and **11**, however, were close to theirs, forcing the conclusion that the high selectivity is imposed in some way

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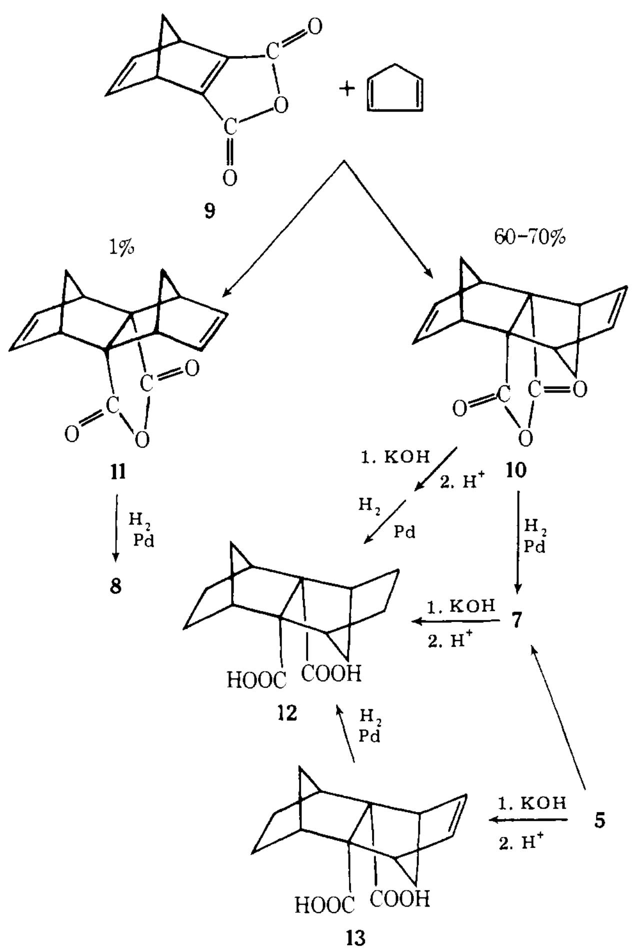
Scheme II



by the extra double bond in **9** compared to **4**. This point is discussed further below.

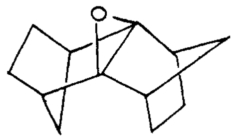
Catalytic hydrogenation separately of **5** to **7** and **6** to **8** was followed by a series of attempts to hydrolyze the anhydrides to the corresponding dibasic acids. Both **5** and **7** could be hydrolyzed in 2 h with 3 equiv of KOH in a 3:1 ethanol-water solution at 60-80 °C. However, when **6** or **8** was similarly treated at 85-100 °C overnight with 6 equiv of KOH, only starting material was recovered. This served as a quantitative way of separating mixtures of **5** and **6** or of **7** and **8** instead of the thin layer chromatography used at first.

Despite indications in a similarly constituted compound,[7] hot sulfuric acid of various strengths was also unavailing for the hydrolysis of the syn anhydride.

There is evidently also hindrance in many of the reactions which might be used to convert the saturated dicarboxylic acid **12** into anti sesquinorbornene **1**. Lead tetraacetate and pyridine[8] in reaction with **12** or its dipotassium salt yielded only dehydration to anhydride **7** in Me_2SO or benzene. The same was true of treatment of **12** with cuprous oxide and bipyridyl in quinoline.[9] Although the anhydride **7** reacted with sodium *tert*-butyl peroxide to yield the mono-*tert*-butylperoxy ester of **12**, no route was found to the bis-*tert*-butyl peroxy ester. Attempts to form the bis acid chloride of **12** led only back to the anhydride **7**. The syn anhydride **8** was impervious to attack by sodium *tert*-butyl peroxide. Attempts to photolyze **7** directly to **1** were unsuccessful. Also unsuccessful was an attempt to convert **8** directly into **2** by sublimation at 1-mm pressure into a hot wire chamber at 450-500 °C. Treatment of **8** with tris(triphenylphosphine)rhodium chloride[10] or of **7** with bis(triphenylphosphine)nickel dicarbonyl[11] only returned the starting anhydride.

Synthesis of **1** in 20% yield was accomplished by electrolysis of **12** in 10% aqueous pyridine using platinum electrodes.[12] **1** is a white solid, mp 64-65 °C, bp 40 °C (0.6 mm). Its symmetric structure is reflected in its four well-resolved ^{13}C NMR absorptions at 153.86, 56.51, 41.39, and 26.57 ppm. Its ^1H NMR spectrum shows absorptions at δ 2.82 (s, 4 H) and 0.90-1.80 (m, 12 H).

anti-Sesquinorbornene (**1**) proved inert to singlet oxygen generated chemically from triphenyl phosphite ozonide.[13] However, as in the case of dehydrojanusene (B), photooxygenation with the 450-W Hanovia mercury vapor lamp (in chloroform solvent, with tetraphenylporphin as sensitizer) led to consumption of **1** in 2.5 h. A mixture of products including 25-40% of the epoxide **14** was produced, but no dioxetane.



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Epoxide **14** was identified by its VPC retention time, compared with an authentic specimen prepared by *m*-chloroperbenzoic acid epoxidation of the olefin **1**.

It is evident that **1** does not react directly with singlet oxygen, but does react with some of the further intermediates produced from typical photosensitizers in the light of a mercury vapor lamp.

In contrast to its slowness in reaction with singlet oxygen, **1** reacted completely in 50 min of photooxidation in benzene with biacetyl as sensitizer[14] in the light of a Hanovia 450-W mercury lamp. The sole product was the epoxide **14** identical with that from peracid epoxidation. The epoxide, a waxy solid melting at 41-44 °C, has absorptions in the ^1H NMR at 2.60, 2.46, 1.80-1.20, 0.68, and 0.60 ppm. The ^{13}C NMR spectrum exhibits the seven absorptions, expected from its symmetry, at 66.72, 54.01, 40.93, 37.73, 33.91, 27.69, and 25.83 ppm.

The extent to which normal reaction of singlet oxygen takes precedence over the formation of other intermediates under such conditions is shown by a competition experiment between **1** and biadamantylidene (A) in photooxidation sensitized by tetraphenylporphine. In the absence of A, **1** reacted only in 3.5 h to give epoxide and other products, but no dioxetane. In the competition experiment, A was almost completely converted to dioxetane in 5 min, while no detectable amount of **1** had reacted in that time.

It has been observed previously[14] that photoepoxidation is far less sensitive to structure of the olefin than is reaction with singlet oxygen. Competition experiments in the photoepoxidation with biacetyl were not very reproducible, especially with β-methylstyrene, where direct energy transfer is known to play a special role.[14] Rough relative reactivities from a series of such competitions with norbornene as a standard follow: 2,3-dichloronorbornene, 0.1; biadamantylidene, 0.8; norbornene, 1.0; sesquinorbornene, 2.6.

Crystal Structure Determination. Molecular dimensions of the three anhydrides **6**, **7**, and **8** were determined by X-ray crystallographic technique described in a recent paper.[4]

Saturated Syn Anhydride 8. A crystal 0.15 × 0.40 × 0.45 mm was used to collect all data. The unit cell was found to be orthorhombic and the space group $P2_12_12_1$ with a = 11.870 (5) Å, b = 12.779 (6) Å, c = 7.409 (3) Å, V = 1123.8 Å^3, Z = 4, d_c = 1.373 g cm^{-3}, and μ = 7.32 cm^{-1}. A total of 934 independent reflections were collected, of which 899 had intensities greater than $3\sigma(I)$. The structure was refined to a conventional R factor of 0.067 using all 934 reflections. Atomic positional parameters are given in Table I. A final difference map showed a largest peak of 0.26 e/Å^3.

Unsaturated Syn Anhydride 6. Crystals of this anhydride decompose quite rapidly upon exposure to X-rays. Intensity

Table I. Coordinates (Å) for Saturated Syn Anhydride **8**[a]

atom	x	y	z
C(1)	1.0742	0.0179	4.6173
C(2)	2.0820	0.6326	3.6252
C(3)	1.1977	1.1182	2.4494
C(4)	−0.2338	0.7463	2.9058
C(4a)	−0.6196	1.6804	4.0831
C(5)	−2.0784	1.6204	4.6669
C(6)	−2.2173	2.7002	5.7805
C(7)	−1.3615	2.1597	6.9311
C(8)	−0.7763	0.8498	6.3732
C(8a)	0.2457	1.1706	5.2545
C(9)	−2.0285	0.3693	5.5708
C(10)	0.0914	−0.5827	3.6022
C(11)	1.1371	2.3654	5.6190
C(12)	−0.1935	3.1245	3.8631
O(13)	0.8262	3.4209	4.7840
O(14)	1.9479	2.4702	6.4555
O(15)	−0.5733	3.9155	3.1110
H(1)	1.531	−0.741	5.238
H(2a)	2.754	1.304	3.897
H(2b)	2.754	0.000	3.319
H(3a)	1.365	2.070	2.052
H(3b)	1.472	0.741	1.423
H(4)	−1.056	0.626	2.223
H(5)	−2.766	1.648	3.823
H(6a)	−1.970	3.591	5.609
H(6b)	−3.181	2.786	6.009
H(7a)	−0.582	2.850	7.179
H(7b)	−1.970	1.968	7.802
H(8)	−0.546	0.281	7.068
H(9a)	−1.852	−0.537	5.023
H(9b)	−2.789	0.319	6.142
H(10a)	−0.641	−1.073	3.993
H(10b)	0.653	−1.214	2.971

[a] Fractional coordinates and standard deviations included in the supplementary material.

Table II. Coordinates (Å) for Unsaturated Syn Anhydride **6**[a]

atom	x	y	z
C(1)	8.9212	14.9941	8.7707
C(2)	8.0262	15.4151	7.5707
C(3)	6.8080	14.7843	7.7173
C(4)	6.9035	13.9466	9.0014
C(4a)	7.8684	12.7539	8.6423
C(5)	8.1632	11.6202	9.6855
C(6)	9.0616	10.5900	8.9571
C(7)	10.4196	11.2710	8.8151
C(8)	10.1732	12.6735	9.4605
C(8a)	9.2513	13.4465	8.4798
C(9)	9.2305	12.2611	10.6072
C(10)	7.8102	14.8906	10.0730
C(11)	9.6070	13.2410	7.0480
C(12)	7.5541	12.2007	7.2843
O(13)	8.6034	12.5010	6.3968
O(14)	10.5386	13.6060	6.4207
O(15)	6.6142	11.6231	6.8752
H(1)	9.773	15.519	9.148
H(2)	8.306	16.021	6.727
H(3)	5.952	14.858	7.057
H(4)	6.174	13.651	9.489
H(5)	7.281	11.366	10.239
H(6a)	8.749	10.259	8.034
H(6b)	9.150	9.685	9.546
H(7a)	10.701	11.366	7.784
H(7b)	11.185	10.734	9.353
H(8)	11.061	13.047	9.841
H(9a)	8.873	13.047	11.272
H(9b)	9.704	11.596	11.159
H(10a)	8.029	14.570	10.819
H(10b)	7.531	14.599	10.239

[a] Fractional coordinates and standard deviations are included in the supplementary material.

data were collected at the maximum scan rate on a crystal of dimensions 0.25 × 0.15 × 0.35 mm. Intensity data were corrected for decomposition by linear interpolation between periodically monitored reference reflections. The unit cell was found to be orthorhombic and the space group *Pbca* with a = 13.843 (4) Å, b = 14.369 (6) Å, c = 11.364 (4) Å, V = 2260.2 (9) Å^3, Z = 8, d_c = 1.353 g cm^{-3} and μ = 7.28 cm^{-1}. A total of 1601 independent reflections were measured, of which 1121 had intensities greater than $3\sigma(I)$. The structure was refined to a conventional R factor of 0.097 using the 1121 reflections with $I > 3\sigma(I)$. Atomic positional parameters are shown in Table II.

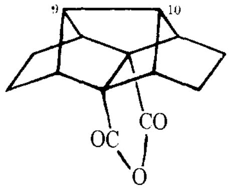
Saturated Anti Anhydride 7. The crystal dimensions were 0.45 × 0.35 × 0.25 mm. The space group was *Pn*, with unit cell dimensions a = 10.706 (3) Å, b = 7.259 (2) Å, c = 7.394 (2) Å, β = 93.12 (2)°, V = 573.8 (3) Å^3, Z = 2, d_c = 1.344 g cm^{-3}. The independent reflections numbered 862, of which 812 had intensity greater than $3\sigma(I)$. The structure was refined to a conventional R factor of 0.0374, using 812 reflections. The largest peak in the final difference map was 0.17. Atomic positional parameters are given in Table III.

Table IV compares some significant interatomic distances in the three anhydrides, and Table V compares some bond angles in these compounds.

Discussion

No conditions were found under which the syn-saturated anhydride **8** or the syn-unsaturated anhydride **6** could be hydrolyzed to the corresponding dibasic acid, a reaction which occurred cleanly with potassium hydroxide on the anti anhydride **7**. A glance at the structural formula of **8** suggests that the two syn ethylene bridges are so arranged in space as to block access of any nucleophile to the anhydride carbonyl group. Quantitative support for this view is afforded by the interatomic distances shown in Table IV. The carbonyl C(11) is located almost on a straight line between the two endo hydrogens attached to C(2) and C(7); thus the p orbital of C(11) that must be engaged by the approaching hydroxyl ion extends toward these two hydrogen atoms and meets them at a distance of 2.60 Å. This distance is less than the sum of the normal van der Waals radii of C═O and H, and leaves no room on the preferred approach path of the hydroxyl ion. One way of overcoming this hindrance might be an accommodation of the molecule as a whole to a spreading apart of the ethylene bridges sufficient to permit incipient bond formation between the approaching nucleophile and C(11). Such a distortion would inevitably press the bridges on the opposite side of the molecule closer together, but, as seen in Table IV, the endo-H-H distance between the methylene groups 9 and 10 is already a mere 1.68 Å, so much less than the van der Waals sum that it probably represents a time average of two skewed repulsive conformations. The molecule of **8** is thus fortified against any breaching of its steric hindrance.

A second way of overcoming this barrier is suggested[7] by the case of the related molecule **15** which resembles **8** in the



15

placement of the hindering hydrogen atoms. Whereas **15** was not hydrolyzed by alkali, it was converted into the dibasic acid by sulfuric acid, implying perhaps that the protonation of one anhydride carbonyl liberated the other as an acyl cation, with

Table III. Coordinates (Å) for Saturated Anti Anhydride **7**[a]

atom	*x*	*y*	*z*
C(1)	2.0470	3.7239	2.4526
C(2)	0.5824	3.4429	2.0282
C(3)	−0.1938	4.6276	2.5909
C(4)	0.9304	5.4413	3.3192
C(4a)	1.8425	6.1339	2.3136
C(5)	1.2869	6.9048	1.0603
C(6)	2.4827	7.5834	0.4141
C(7)	3.2589	6.3836	−0.1804
C(8)	2.4356	5.1807	0.1775
C(8a)	2.6101	4.9499	1.7243
C(9)	1.0074	5.7709	0.0340
C(10)	1.8736	4.3198	3.8538
C(11)	4.0362	5.1575	2.2485
C(12)	2.8949	6.9106	3.1173
O(13)	4.1432	6.3320	2.9879
O(14)	4.9943	4.4664	2.1265
O(15)	2.7846	7.8593	3.8175
H(1)	2.644	2.889	2.373
H(2b)	0.310	2.497	2.499
H(2a)	0.418	3.325	1.131
H(3b)	−0.717	4.370	3.305
H(3a)	−0.749	5.147	1.945
H(4)	0.632	6.141	3.963
H(5)	0.514	7.491	1.242
H(6a)	3.083	8.116	0.932
H(6b)	2.098	8.304	−0.348
H(7a)	4.325	6.417	0.096
H(7b)	3.255	6.475	−1.161
H(8)	2.612	4.312	−0.303
H(9b)	0.846	6.170	−0.872
H(9a)	0.203	5.168	0.192
H(10a)	2.751	4.551	4.414
H(10b)	1.435	3.637	4.547

[a] Fractional coordinates and standard deviations are included in the supplementary material.

Table IV. Interatomic Distances (Å) in Anhydrides **6**, **7**, and **8**

	6	**7**	**8**
C(8a)-C(1)	1.610(9)	1.548(6)	1.556(8)
C(1)-C(2)	1.550(10)	1.528(8)	1.542(9)
C(2)-C(3)	1.379(11)	1.540(8)	1.549(10)
C(3)-C(4)	1.536(10)	1.538(7)	1.547(9)
C(4)-C(4a)	1.575(10)	1.557(6)	1.552(8)
C(4a)-C(5)	1.568(9)	1.548(5)	1.573(8)
C(5)-C(6)	1.549(9)	1.548(7)	1.558(9)
C(6)-C(7)	1.527(10)	1.565(7)	1.534(10)
C(7)-C(8)	1.563(10)	1.513(7)	1.538(9)
C(8)-C(8a)	1.553(10)	1.564(4)	1.549(8)
C(4a)-C(8a)	1.554(9)	1.546(5)	1.543(8)
C(5)-C(9)	1.549(9)	1.544(6)	1.545(9)
C(8)-C(9)	1.541(10)	1.545(5)	1.563(8)
C(1)-C(10)	1.542(10)	1.542(7)	1.535(9)
C(4)-C(10)	1.558(10)	1.542(7)	1.535(9)
C(8a)-C(11)	1.489(9)	1.506(6)	1.534(9)
C(4a)-C(12)	1.500(8)	1.504(6)	1.522(8)
C(11)-O(13)	1.406(9)	1.388(6)	1.382(8)
C(12)-O(13)	1.406(8)	1.389(6)	1.405(8)
C(11)-O(14)	1.182(10)	1.194(6)	1.169(9)
C(12)-O(15)	1.177(9)	1.188(5)	1.156(8)
C(1)-H(1)[a]	1.02	1.02	1.08
C(2)-H(2)endo[a]	1.09	0.95	1.02
C(2)-H(2)exo[a]		1.03	1.05
C(5)-H(5)[a]	1.07	1.00	1.01
C(6)-H(6)endo[a]	1.08	1.02	1.02
C(6)-H(6)exo[a]	1.06	1.04	1.04
C(9)-H(9)exo	0.98	1.00	0.96
C(9)-H(9)endo	1.09	1.03	1.08
C(10)-H(10)exo	1.12	1.08	1.06
C(10)-H(10)endo	1.04	1.04	0.96
C(11)-H(2)[a]	3.10		2.60
C(11)-H(7)[a]	2.35	2.52	2.46
H(9)-H(10)	1.80		1.68
O(13)-H(10)[b]		2.72	
C(11)-H(10)[b]		2.67	
H(9)-H(2)[b]		2.08	

[a] Equivalent bonds averaged. [b] Interactions in anti anhydride.

potential reactivity in any direction perpendicular to the CO axis. We did not succeed in hydrolyzing **8** under these conditions. It seems likely that **15**, with C(9) and C(10) only 1.54 Å (the C-C bond length) apart, has the needed flexibility in marginally spreading the ethylene bridges pressing against the anhydride ring. The changes with structure in all the related angles, as shown in Table V, are consistent with this.

Figure 1 shows the dihedral angles between the least-squares planes corresponding to the bridges in **6**, **7**, and **8**. The greatest visible effect of the double bond in **6** is to reduce the "cyclohexane" dihedral angle of 114.2° to the "cyclohexene" dihedral angle of 109.0°. In **6** and **8**, which have methylene bridges juxtaposed, the planes of these bridges diverge from each other by 19.3 and 19.6°, while in the anti isomer **7** the divergence between the planes of the juxtaposed methylene and ethylene bridges is reduced to 11.9°. This relaxation of about 7.5° is taken up fairly evenly by the other angles in the molecule. The tilt of the anhydride ring in its cavity in the anti isomer **7** is 3° more toward the methylene than the ethylene bridge. Thus the anti anhydride has not only less hindrance to approach of a reactant, but greater flexibility in adjusting to that approach.

Reactivity Pattern of the Olefin 1. *anti*-Sesquinorbornene (**1**) is a tetraalkylethylene and might be expected to have a general reactivity comparable to that of tetramethylethylene except, of course, for the stereochemical prohibition of the ene reaction. Other things being equal, *anti*-sesquinorbornene might be expected to yield a dioxetane with singlet oxygen with about the reactivity with which tetramethylethylene yields an allylic hydroperoxide—especially in view of evidence that the transition states for dioxetane formation and ene reaction are similar.[15] With respect to photoepoxidation sensitized by biacetyl the reactivity of **1** indeed appears to be about 2.6 times that of biadamantylidene, and **1** is normally reactive toward *m*-chloroperbenzoic acid. Yet under a variety of conditions no trace of dioxetane nor of any apparently singlet oxygen derived product has been obtained from **1**. What is the meaning of this special hindrance?

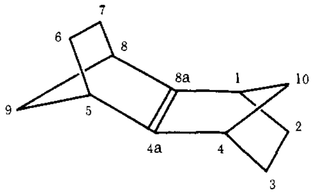
In fact, this selective behavior fits uniquely well with the mechanism of singlet oxygen addition as it is presently understood. The addition of singlet oxygen to the carbon-carbon double bond is a concerted molecular reaction, with two closely related allowed geometries of approach, the (2s + 2a) addition and the (2 + 1) perepoxide formation. Both of these approaches require the O_2 molecule to enter in a plane perpendicular to the C=C bond and equidistant from the two carbons. In biadamantylidene this approach allows the oxygen atoms to occupy the most open part of the molecule. In **1**, however, it requires the oxygen molecule to enter by a path blocked on one side by endo-H(9) and on the other by the ethylene bridge.

How serious this blocking is can be seen from the coordinates of the atoms in **1**, shown in Table VI. In the absence of a direct X-ray crystallographic study of the olefin, coordinates have been calculated by assuming that each norbornene ring has the bond lengths and angles observed for the norbornene ring in **6** and that the bridgehead atoms 1, 4, 5, and 8 lie in a common plane with the double-bonded 4a and 8a, this being taken as the *xy* plane. From the resulting coordinates it can be determined that endo-H(10) is just 3.29 Å from both H(6) and H(7), the latter two being 2.25 Å apart. Figure 2 shows a top view of the *xy* plane containing the double bond, with the *x* and *y* coordinates of the three hydrogen atoms in front of it. Around

Table V. Bond Angles (deg) in Anhydrides **6**, **7**, and **8**

	6	**7**	**8**
C(8a)C(1)C(2)	104.0(5)	112.5(4)	108.4(4)
C(1)C(2)C(3)	107.3(5)	104.6(4)	103.9(5)
C(2)C(3)C(4)	106.5(5)	102.1(4)	103.3(5)
C(3)C(4)C(4a)	105.1(5)	111.6(3)	108.0(4)
C(4)C(4a)C(8a)	103.4(5)	103.1(3)	103.8(4)
C(4a)C(8a)C(1)	102.8(5)	103.1(3)	103.4(4)
C(8a)C(1)C(10)	102.2(5)	100.6(3)	102.7(4)
C(2)C(1)C(10)	98.6(5)	99.7(3)	98.6(4)
C(1)C(10)C(4)	94.5(5)	93.7(3)	95.6(4)
C(3)C(4)C(10)	99.1(5)	101.3(3)	98.4(4)
C(4a)C(4)C(10)	103.0(5)	100.3(3)	103.3(4)
C(4a)C(5)C(6)	106.1(5)	107.8(3)	108.8(4)
C(5)C(6)C(7)	105.2(5)	103.5(4)	104.0(5)
C(6)C(7)C(8)	102.8(5)	103.4(3)	103.9(5)
C(7)C(8)C(8a)	106.3(5)	108.6(3)	109.7(4)
C(8)C(8a)C(4a)	103.9(5)	103.5(3)	104.3(4)
C(8a)C(4a)C(5)	103.0(5)	103.7(3)	103.1(4)
C(4a)C(5)C(9)	103.1(5)	102.5(3)	102.6(4)
C(6)C(5)C(9)	99.0(5)	99.2(3)	98.4(4)
C(5)C(9)C(8)	95.1(5)	95.0(3)	94.4(4)
C(7)C(8)C(9)	99.5(5)	100.8(3)	98.3(4)
C(8a)C(8)C(9)	103.9(5)	101.5(2)	102.8(4)
C(4a)C(8a)C(11)	104.6(5)	104.0(3)	104.4(4)
C(8a)C(11)O(13)	110.3(5)	110.3(3)	108.7(4)
C(11)O(13)C(12)	110.6(4)	111.0(3)	113.5(4)
O(13)C(12)C(4a)	109.6(5)	109.9(3)	108.0(4)
C(12)C(4a)C(8a)	104.8(5)	104.6(3)	105.4(4)
C(8a)C(11)O(14)	131.0(5)	129.4(3)	130.0(5)
O(13)C(11)O(14)	118.7(5)	120.4(3)	121.3(5)
C(4a)C(12)O(15)	131.5(5)	130.0(3)	130.7(5)
O(13)C(12)O(15)	118.8(5)	120.1(3)	121.4(5)
C(1)C(8a)C(11)	111.0(5)	107.9(3)	111.4(4)
C(8)C(8a)C(11)	113.3(5)	112.1(3)	111.9(4)
C(4)C(4a)C(12)	110.9(5)	107.6(3)	113.1(4)
C(5)C(4a)C(12)	112.0(5)	112.6(3)	110.5(4)
C(4)C(4a)C(5)	120.7(5)	123.2(3)	119.3(4)
C(1)C(8a)C(8)	119.3(5)	124.0(3)	119.6(4)

Table VI. Atomic Coordinates of *anti*-Sesquinorbornene (**1**)



atom	*x*	*y*	*z*
C(1)	1.477	1.138	0
C(2)	2.003	0.777	−1.460
C(3)	2.003	−0.777	−1.460
C(4)	1.477	−1.138	0
C(4a)	0	−0.690	0
C(5)	−1.477	−1.138	0
C(6)	−2.003	−0.777	1.460
C(7)	−2.003	0.777	1.460
C(8)	−1.477	1.138	0
C(8a)	0	0.690	0
C(9)	−2.072	0	−0.869
C(10)	2.072	0	0.869
endo-H(6)	−1.364	−1.127	2.216
endo-H(7)	−1.364	1.127	2.216
endo-H(10)	1.708	0	1.854

these three hydrogen atoms have been drawn circles indicating the normal van der Waals radii of these atoms (1.2 Å); it is obvious that the π system of the double bond, which lies 1.85–2.22 Å below these obstructing hydrogen atoms, cannot be approached by an oxygen atom coming from above. Indeed, the aperture is only about one-third large enough to permit the passage of an oxygen atom with its radius of 1.4 Å. The prohibition against any concerted reaction of a reagent with the π system as a whole would appear to be total.

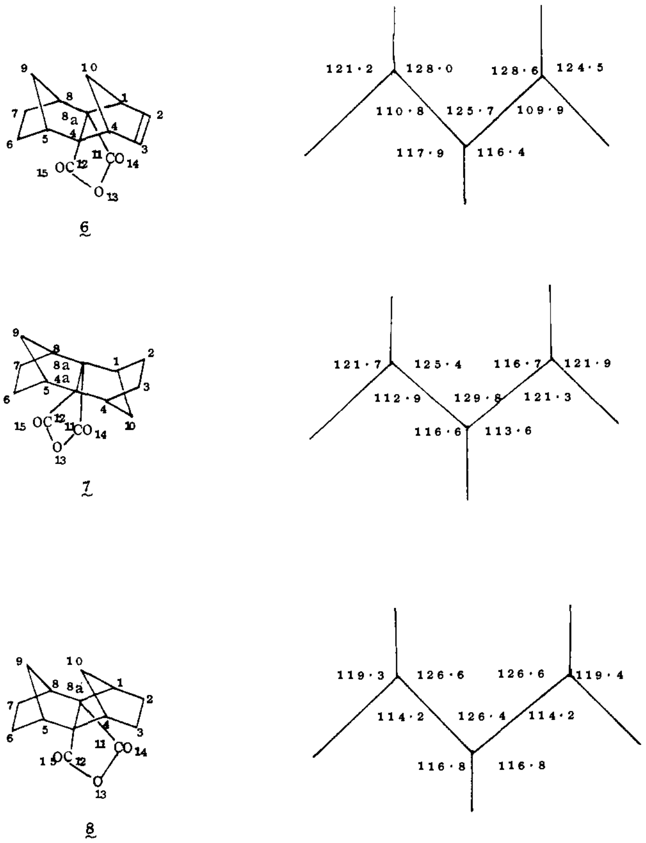


Figure 1. Dihedral angles between least-squares planes in **6**, **7**, and **8**. Projections on the plane containing C(9), C(10), and O(13).

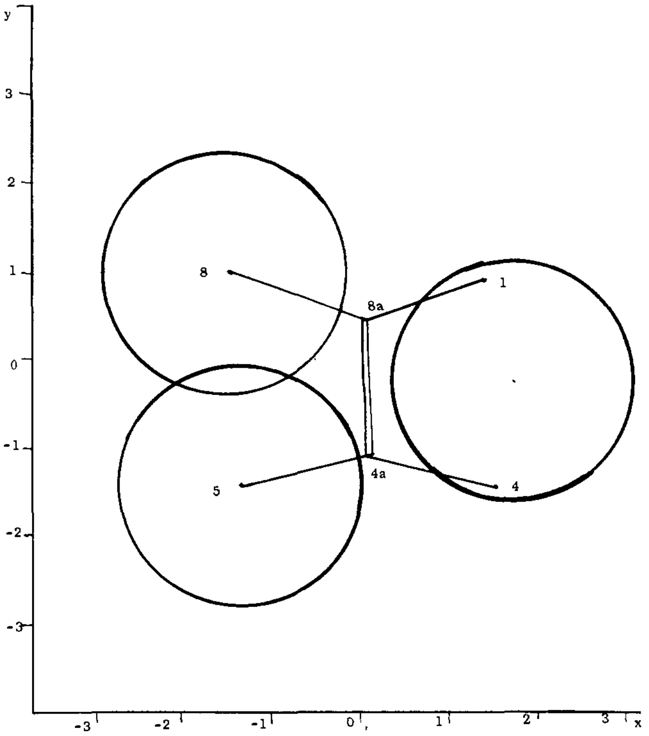
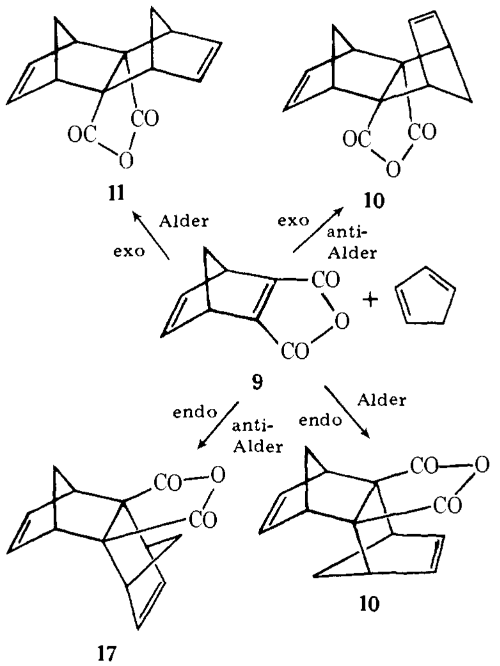


Figure 2. View from above toward the C=C bond of **1**. Circles represent 1.2-Å van der Waals radius of blocking hydrogen atoms H(6), H(7), and H(10).

What mechanisms remain, then, for the reactions of the double bond that still occur in this inhospitable model com-

Scheme III



pound? From Figure 2 and similar diagrams it can be seen that if, instead of concerted reaction with the π system as a whole, reaction can be initiated by bond formation with the p orbital on one of its carbon atoms, there is an unhindered approach in the *yz* plane at an angle of 45° from the vertical to either C(4a) or C(8a). By an approach somewhat to the right of the *yz* plane this open angle can be as small as 38° without any invasion of the van der Waals radii of the H's or the entering O.[17]

Accordingly, the olefin **1** may be capable of affording important information about where in the range of reaction mechanisms a particular reaction falls. The information about the stereochemistry of **1**, coupled with the emphatic evidence of dichotomy between singlet oxygen addition and epoxidation, tells us that, whatever chain of events may be involved in the photosensitized and other epoxidation, the reaction is a stepwise process with effective attack on one end of the double bond at a time. This conclusion also fits generally with the observed loss of configuration in photoepoxidation in contrast to the retention in dioxetane formation. We note further that, whereas peracid epoxidation is often stereospecific, suggesting a concerted process, the ability of peracids to epoxidize **1** probably means that a peracid is not limited to a concerted mechanism under all circumstances.

Bicyclic Structure and Dienophilic Activity. Edman and Simmons[5] made the striking observation that norbornadiene-2,3-dicarboxylic anhydride (**9**) reacted with cyclopentadiene to yield 60–70% of the anti anhydride **10** and only 1% of its syn isomer **11**. The greatly preferred isomer might have been the result of either exo attack on the dienophile in the anti-Alder manner or endo attack in accordance with Alder's rule (Scheme III). By an ingenious experiment using deuterated cyclopentadiene, Edman and Simmons concluded that the greatly preferred path was the exo-anti-Alder attack.

A new puzzle appears in our observation that, when the dienophile is norbornene-2,3-dicarboxylic anhydride (**4**), the corresponding anti and syn isomers are formed in the ratio of 3:2 rather than 60:1. The correspondence in structure between our isomers and those of Edman and Simmons was confirmed by the identity of the fully hydrogenated products **7** and **8** made by hydrogenation of our anhydrides **5** and **6** and alternatively by hydrogenation of **10** and **11** made from the norbornadiene anhydride. If we assume that with **4**, as with the more unsaturated dienophile **9**, cyclopentadiene adds to the exo side of the molecule, we must explain a 40-fold effect on the orientation of addition by a double bond so remote from the scene of the action that it would not be expected to be effective in either a polar or a steric sense. Work is continuing on this problem.

Experimental Section

Dimethyl acetylenedicarboxylate, dicyclopentadiene, 2,3-butanedione, and *m*-chloroperbenzoic acid were obtained from the Aldrich Chemical Co. Cyclopentadiene was from freshly cracked dicyclopentadiene and was redistilled before use. Ether was distilled from sodium benzophenone ketyl. All other solvents were spectral grade from Aldrich and were used without further purification. The silica gel used in the Diels-Alder reaction was 60 Pf-254 for preparative thin layer chromatography made by EM Reagents and obtained from Brinkmann Instruments, Inc. NMR spectra were obtained from JEOL MH 100 and JEOL-FX60 NMR spectrometers in $CDCl_3$ with internal Me_4Si as reference unless otherwise noted. Infrared spectra were taken on a Perkin-Elmer 197 infrared spectrophotometer. Melting points are uncorrected and were taken on a Hoover capillary melting point apparatus. Gas chromatographic analyses were done using a 10-ft 5% SE-30 column.

Bicyclo[2.2.1]hept-2-ene-2,3-dicarboxylic Acid (3). Compound **3** was made by an adaptation of the procedure of Diels and Alder.[16] Cyclopentadiene (16.17 g, 0.245 mol) was added dropwise to dimethyl acetylenedicarboxylate (34.2 g, 0.241 mol) at 0 °C. After stirring for 1 h, the crude diester was hydrogenated in EtOH (100 mL) and 10–20 psi in a Parr shaker apparatus using 5% Pd/charcoal as catalyst. The catalyst was filtered and the filtrate transferred to a 500-mL three-necked flask with another 200 mL of EtOH. KOH (33.74 g, 0.6025 mol) was added and the solution stirred and refluxed for 1.5 h. The resultant slurry was cooled and 150 mL of water added to dissolve the potassium salts. The solution was acidified with sulfuric acid and the precipitated potassium sulfate was filtered off. The liquid was removed from the filtrate in vacuo and the residue dissolved in 150 mL of 2 N NaOH solution. The basic solution was extracted three times with ether and acidified with sulfuric acid. The precipitated diacid was collected by filtration, washed three times with water, and dried to yield 30.3 g (60% from dimethyl acetylenedicarboxylate) of diacid **3**, mp 213–214 °C (lit. 212 °C).[16]

Bicyclo[2.2.1]hept-2-ene-2,3-dicarboxylic Acid Anhydride (4).[16] Acetic anhydride (104 mL) was added rapidly dropwise to **3** (29.2 g, 0.16 mol), refluxed for 1.5 h, and cooled. The excess acetic anhydride and the acetic acid were distilled out under reduced pressure. The flask was cooled and the residue recrystallized twice from ether to yield 22.8 g (87%) of **4** (mp 96–97 °C, lit. 98–99 °C).[16]

1,2,3,4,4a,5,8,8a-Octahydro-1,4,5,8-*exo,endo*-dimethanonaphthalene-4a,8a-dicarboxylic Anhydride (5) and 1,2,3,4,4a,5,8,8a-Octahydro-1,4,5,8-*exo,exo*-dimethanonaphthalene-4a,8a-dicarboxylic Anhydride (6). Compound **4** (5 g, 0.031 mol) was adsorbed on silica gel[6] (50 g) by evaporation under reduced pressure of a slurry of methylene chloride, **4**, and silica gel. Freshly distilled cyclopentadiene was added until all of the silica was wet. The new slurry was agitated by means of a magnetic stirrer for 2 h. The slurry was washed into a sintered glass funnel and washed nine to ten times with chloroform. From the filtrate the cyclopentadiene polymer(s) distilled out (bp 60–80 °C, 5 mm) to give **5** and **6** (crude yield 84%) in a ratio of approximately 3:2. Compounds **5** and **6** may be isolated pure by repeated thin layer chromatography on silica gel using a 3:13 mixture (v:v) of chloroform-benzene. Compounds **5** and **6** could also be separated chemically as detailed in the procedure for synthesis of **13**. Compound **5** gave ^1H NMR absorptions at δ 6.36 (s, 2 H), 3.42 (s, 2 H), 2.62 and 2.72 (3 H total), 1.20–1.80 (m, 6 H), 1.02 and 1.12 (1 H total). Compound **5** had ^{13}C absorptions at 174.71, 137.55, 66.73, 50.03, 40.67, 39.31, and 28.07 ppm. Compound **5** melted at 197–199 °C. The significant bands in the IR ($CDCl_3$) were at 1857 and 1773 cm^{-1}. Compound **6** gave absorptions in the ^1H NMR at δ 6.46 (s, 2 H), 3.28 (s, 2 H), 2.76 (s, 2 H), 2.40–2.64 (m, 2 H), 1.36–1.88 (m, 6 H). Compound **6** had ^{13}C absorptions at 173.48, 140.02, 67.70, 49.83, 48.54, 41.39, 41.06, and 27.55 ppm. Compound **6** melted at 191–193 °C and had IR absorptions ($CDCl_3$) at 1854 and 1771 cm^{-1}.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-1,4,5,8-*exo,endo*-dimethanonaphthalene-4a,8a-dicarboxylic Anhydride (7). Method A. Compound **5** was hydrogenated at 15 psi in ethyl acetate in a Parr shaker apparatus using 5% Pd/charcoal as catalyst to give **7**.

Method B. **12** (0.5 g, 0.002 mol) was placed in a 5-mL round-bottomed flask. Thionyl chloride (2 mL) was added dropwise with cooling and magnetic stirring. The ice bath was removed and the solution was stirred for 1 h. Excess $SOCl_2$ was removed by rotary evaporation, and the residue was purified by thin layer chromatography (silica gel, Et_2O) to give 0.43 g (93%) of **7**.

Compound **7** had ^{1}H NMR absorptions at δ 2.80 (s, 2 H), 2.65 (s, 2 H), 2.16 (s, 0.5 H), 2.04 (s, 0.5 H), and 1.20–1.88 (m, 11 H) and ^{13}C absorptions at 175.59, 65.23, 44.31, 39.60, 39.18, 38.89, 27.32, and 23.78 ppm. Compound **7** melted at 190–193 °C and had IR absorptions at 1861 and 1773 cm^{-1}.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-1,4,5,8-*exo,exo*-dimethanonaphthalene-4a,8a-dicarboxylic Anhydride (8). Compound **8** was prepared by hydrogenation of **6** under conditions described above. Compound **8** exhibited ^{1}H NMR absorptions at δ 2.66 (m, 3 H), 2.46 (s, 1 H), and 1.16–1.80 (m, 10 H) with ^{13}C absorptions at 174.45, 69.20, 43.01, 41.48, and 27.54 ppm. Compound **8** had IR absorptions ($CDCl_3$) at 1851 and 1773 cm^{-1} and melted at 185–185.6 °C.

1,2,3,4,4a,5,8,8a-Octahydro-1,4,5,8-*exo,endo*-dimethanonaphthalene-4a,8a-dicarboxylic Acid (13). A crude mixture of **5** and **6** (11.6 g, 0.05 mol) was heated in EtOH–water with KOH (7.2 g, 0.129 mol) as described below for **12**. The initial filtration gave 3.25 g of **4** (28%). Further workup as described below gave a total of 5.5 g (44%) of **13**. Compound **13** had ^{1}H NMR (acetone-d_6) absorptions at δ 6.24 (s, 2 H), 3.24 (s, 2 H), 2.68 (s, 0.5 H), 2.52 (s, 2.5 H), 1.68 (s, 0.5 H), 1.60 (s, 0.5 H), 1.00–1.52 (m, 5 H), 0.60 (s, 0.5 H), and 0.50 (s, 0.5 H), with ^{13}C absorptions (acetone-d_6) at 180.04, 138.72, 66.73, 56.40, 51.07, 45.16, 32.81, and 28.91 ppm. Compound **13** charred over a 110–130 °C range.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-1,4,5,8-*exo,endo*-dimethanonaphthalene-4a,8a-dicarboxylic Acid (12). Method A. Compound **7** (6.6 g, 0.0284 mol) was dissolved in 75 mL of a 3:1 (v/v) mixture of EtOH–water with KOH (3.97 g, 0.071 mol) and maintained at 60–80 °C for 2 h. The solution was cooled and then evaporated to near dryness. Water (50 mL) was added and the liquid filtered. The filtrate was acidified with HCl and the solid filtered off. The solid was washed with water, dried, and recrystallized from ether–pentane. If an oil formed after acidification, then the aqueous layer was extracted three times with EtOAc. The combined layers were then washed twice with saturated NaCl solution and dried over Na_2SO_4.

Method B. Compound **13** (2.48 g, 0.01 mol) was dissolved in 150 mL of EtOAc and hydrogenated in a Parr shaker apparatus using 5% Pd/charcoal as catalyst to give 2.3 g (92%) of **12** following removal of the EtOAc.

The ^{1}H NMR (acetone-d_6) of a saturated solution of **12** gave very weak absorptions at δ 2.66–2.80 (m), 2.56–2.66 (m), and 1.0–2.0 (m). The ^{13}C spectrum (D_2O with Na_2CO_3, dioxane reference) gave absorptions at 185.23, 165.88, 69.39, 50.68, 43.66, 40.74, 32.81, 28.20, and 25.53 ppm. Compound **12** melted with some decomposition at 206–209 °C.

***anti*-1,2,3,4,5,6,7,8-Octahydro-1,4,5,8-dimethanonaphthalene (1).** Compound **12** (0.8 g, 0.0032 mol) and 0.9 mL of Et_3N were dissolved in 66 mL of 10% aqueous pyridine in a jacketed electrolysis cell. Two platinum gauze electrodes were then placed into the cell and connected to an ammeter, voltmeter, and half-wave rectifier attached to a variable voltage regulator. The cell voltage was cautiously increased until the current was approximately 0.8 A. The initial voltage was 45–55 V dc but rose gradually to about 75 V dc during the course of the reaction even though the setting on the variable voltage regulator was not changed. Carbon dioxide bubbles were observed coming from the solution. The voltage was applied for 8–10 h or until the current had declined to approximately 0.2 A. The solution was poured into water and extracted 11 times with pentane. The combined extracts were washed twice with water, twice with dilute HCl, and twice with saturated NaCl solution and dried over Na_2SO_4. The pentane was removed in vacuo and **1** was purified by VPC on an 8-ft 15% SE-30 on Chromosorb P column at 185 °C. Alternatively, the products of five electrolyses were combined and distilled (40 °C, 0.6 mm) to give 0.5 g (20%) of **1** (mp 64–65 °C). Compound **1** exhibited ^{1}H NMR absorptions at δ 2.8 (s, 4 H) and 0.90–1.80 (m, 12 H) with ^{13}C absorptions at 153.86, 54.51, 41.39, and 26.57 ppm.

1,2,3,4,5,6,7,8-Octahydro-1,4,5,8-*exo,endo*-dimethanonaphthalene 4a,8a-Epoxide (14). Compound **1** (100 mg, 0.000 625 mol) was irradiated for 50 min in a Pyrex test tube with 2,3-butanedione (54 mg, 0.0063 mol) in 8 mL of benzene at 0–5 °C according to the procedure of Shimizu and Bartlett.[14] The solution was concentrated and distilled (bp ~60 °C, 0.04 mm) to give 74 mg (67%) of **15**. Inspection of the ^{1}H NMR and the GC trace indicated that **14** was the sole product from **1**. Trace impurities from starting material were removed by gas-phase chromatography (10 ft 5% SE-30 column) to give a waxy solid melting at 41–44 °C. Compound **14** was also made by oxidation of **1** with 3 equiv of *m*-chloroperbenzoic acid in CH_2Cl_2 for 3.5 h. The ^{1}H NMR had absorptions at δ 2.60 (s, 2 H), 2.46 (s, 2 H), the downfield half of an AB quartet at 1.66 and 1.52, the upfield half of a second AB quartet at 0.60 and 0.68, and a series of overlapping peaks at 1.20–1.80. The ^{13}C spectrum had absorptions at 66.72, 54.01, 40.93, 37.73, 33.91, 27.69, and 25.83 ppm.

Reaction of 1 with Singlet Oxygen. A $CHCl_3$ solution 1.3×10^{-2} M in **1** and 10^{-3} M in tetraphenylporphine was immersed in an ice bath in a Dewar flask and flushed with a stream of oxygen for 5–10 min. The solution was irradiated for approximately 2.5 h with a 450-W Hanovia lamp while continuing the oxygen flow. Ice was replaced in the bath every 0.5 h and water siphoned off without interruption of irradiation. The solution was monitored by gas chromatography for disappearance of **1**. Some sensitizer color changes and bleaching were noticed.

Photooxidation Competition Reactions. A. Norbornene and 1. A $CHCl_3$ solution 1.2×10^{-2} M in **1**, 5.9×10^{-2} M in norbornene, and 1.9×10^{-3} M in tetraphenylporphine with toluene as reference was continuously oxygenated and irradiated at 0 °C with a 450-W Hanovia lamp and monitored by gas chromatography for disappearance of olefins. At a point at which 32% of **1** had been consumed, no detectable decrease in norbornene was observed. Percentage decrease in olefin concentration was determined as follows. A GC trace of the starting material was Xeroxed three times. The olefin and toluene peaks were cut and weighed to determine response factors. The process was repeated with the irradiated samples and the decreases were noted.

B. Ad=Ad and 1. A $CHCl_3$ solution 0.98×10^{-2} M in both olefins and 10^{-3} M in tetraphenylporphine was irradiated as described above with *o*-dichlorobenzene as reference. After 5 min only traces of Ad=Ad remained with no detectable reaction of **1**.

Biacetyl-Sensitized Competitions. Equimolar amounts of norbornene, biacetyl, toluene, and the second olefin were dissolved in benzene to make 0.05 M solutions. The solution was irradiated under the conditions described by Shimizu and Bartlett[14] using a 450-W Hanovia lamp and sampled at intervals. Relative reactivities were determined as described above.

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Supplementary Material Available: Positional parameters, thermal parameters, torsion angles, structure factors, and ORTEP drawings for **6**, **7**, and **8** (29 pages). Ordering information is given on any current masthead page.

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Total Synthesis of (±)-Dendrobine[1,†]

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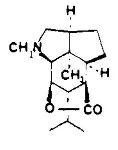
Abstract: A total synthesis of (±)-dendrobine is described. (*E,E,E*)-Triene **9a**, available stereoselectively in six steps from methyl 4-(diethylphosphono)crotonate, cyclizes by an intramolecular Diels-Alder reaction to afford 75-83% of a mixture of four perhydroindanols containing 83% of endo isomers **8a** and **8b**. Epimers **8a** and **8b** were transformed into nitrile **25** by two separate routes, each of which involves epimerization of C4, oxidation, angular methylation, and reductive cyanation. Nitrile **25** served as a precursor of amino ester **3** by two separate routes, the most efficient of which proceeded via bromolactone **40**. Epoxidation of the trichloroethylurethane **58** prepared from **3** afforded a mixture of two epoxides, both of which were utilized in the synthesis. The minor epoxide, **59** (38-40% yields), was transformed into dendrobine via methyl ketodendrobinate **57**, while the major epoxide **60** (45-48% yields) was recycled to **58**. Additional strategies for the synthesis of dendrobine from **3** are discussed.

Dendrobine (**1**) was the first alkaloid to be isolated from *Dendrobium nobile* Lindl, the ornamental orchid thought to be the original plant used to make the Chinese drug "Chin-Shih-Hu".[3,4a] To date, a total of 14 structurally related alkaloids have been isolated from *D. nobile* and other *Dendrobium* species.[4] Structures have been assigned to these alkaloids on the basis of extensive degradation studies, by chemical interconversions, and/or by spectroscopic methods.[4] The structural and pharmacological similarities[4a] between dendrobine and picrotoxinin (**2**) have stimulated interest in the total synthesis of **1**.[5,6] Herein we describe the details of our total synthesis of this alkaloid, a preliminary account of which has been previously reported.[7]



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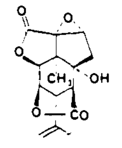
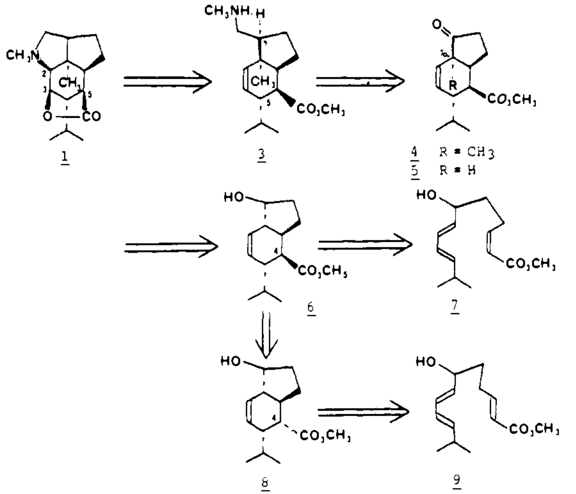


2

Synthetic Strategy

Dendrobine is a challenging synthetic target owing to the presence of seven asymmetric centers on a compact carbon skeleton. Scheme I contains an outline of our analysis of the synthetic problem. It was anticipated that the two heterocyclic rings of the alkaloid could be formed by an oxidative cyclization sequence involving amino ester **3**. The stereocenter at C1 of **3** would be generated by attaching a functionalized one-carbon unit to C1 of ketone **4** with stereochemical induction from the cis ring fusion. Ketone **4** would be prepared by angular methylation of **5**, the generation of a cis fusion being anticipated on the basis of the well-known preference for alkylations of perhydroindanones to afford the cis-fused isomer.[8] As a consequence, the stereochemistry at C7a of **5** and its precursors was of relatively minor strategic importance. Thus, trans-fused hydroxy ester **6** was regarded as a potential precursor of **5**. A trans fusion in **6** was considered to be advantageous since all four stereocenters could be *formally* introduced by the intramolecular Diels-Alder reaction of **7**.[9] However, in that preparation of **6** from **7** would require that **7** cyclize by way of an exo transition state in preference to the endo pathway, which we assumed would be a much more facile process, an alternative route to **6** was sought. The solution arrived at called for the synthesis of **8**, the C4 carbomethoxyl epimer of **6**, by the endo Diels-Alder reaction of **9** in anticipation that **8**, or subsequent intermediates derived therefrom, could be equilibrated with the natural C4 ester epimers.

Scheme I



Synthesis of Triene 9

Having chosen triene **9** to serve as the Diels-Alder substrate, a stereoselective synthesis of this intermediate was sought. Few problems of stereochemical control were anticipated since each olefinic unit in **9** is in its most stable geometrical form. It was anticipated that the dienophilic unit would be introduced using a Wadsworth-Emmons modified Wittig reaction,[10] and that the (*E,E*)-butadiene would be elaborated from methyl (*E,E*)-6-methylhepta-2,4-dienoate (**11a**) (Scheme II).

Sato et al. have reported that treatment of 4-(triethylphosphono)crotonate with NaH and isobutyraldehyde affords the ethyl ester corresponding to **11a** in 52% yield.[11] Attempts

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[†] This paper is dedicated to the memory of the late Professor Robert Burns Woodward in grateful recognition and deepest admiration for his pervasive contribution of example, inspiration, and support.

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