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Unusual Triethylamine Catalyzed Rearrangement of Bicyclic Endoperoxides Derived from Substituted Cycloheptatrienes

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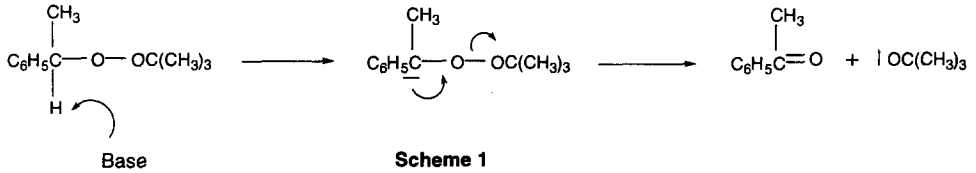
Abstract: Triethylamine catalyzed rearrangement of the substituted bicyclic cycloheptatriene endoperoxides **9, 10,12, 13, 20, 21, 22 and 30** underwent different reaction modes and resulted in the formation of ring contraction products in the case of **9, 10, 12 and 13.** However, **20, 21,** and **30** provided rearranged diketones 23, **24** and **32** almost in quantitative yield. The mechanism of these reactions was discussed. © 1997 Elsevier Science Ltd.

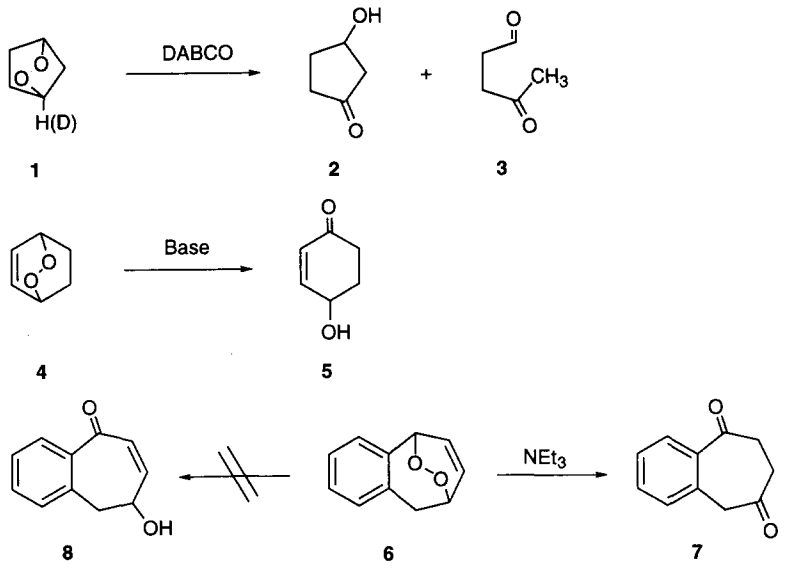
Introduction

The most prevalent base-catalyzed reaction of an endoperoxide is the Kornblum-de la Mare[1] reaction which was reported in 1951. It was found that bases such as potassium hydroxide, sodium ethoxide, or piperidine catalyze the decomposition of 1-phenylethyl *tert*-butyl peroxide (Scheme 1).



Scheme 1

In view of this mechanism, only those dialkyl peroxides and alkyl hydroperoxides having a hydrogen on the carbon attached to the peroxide linkage should undergo base-catalyzed rearrangement. Base-catalyzed decomposition of peroxides and hydroperoxides exemplify a general type of elimination reaction which may be anticipated for compounds in which an anion or group X (capable of giving a relatively stable anion X^-) is attached to oxygen. Zagorski and Salomon have studied base-catalyzed decomposition of **1** in the presence of DABCO and showed on the basis of the observed large negative entropy of activation ($\Delta S = -30 \pm 3$ e.u) and kinetic isotope effect [$k(\mathbf{1}/k\mathbf{1}\text{-}\mathbf{d}_8 = 8$] that the rate-determining step is the removal of bridgehead protons which is in agreement with Kornblum-De La Mare mechanism.[2] The application of this reaction to bicyclic endoperoxides[3] results in the formation of hydroxyketones which can be further converted into interesting compounds like diketones, dienones[4] (Scheme 2). Most recently, we studied the triethylamine-catalyzed reaction of endoperoxide **6** at 0 °C.[5] Surprisingly, we isolated the saturated diketone **7** instead of the expected hydroxy-ketone **8**. In order to reveal the reaction mechanism of this unusual endoperoxide

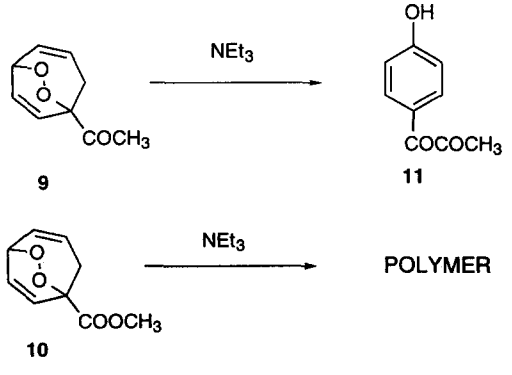


Scheme 2

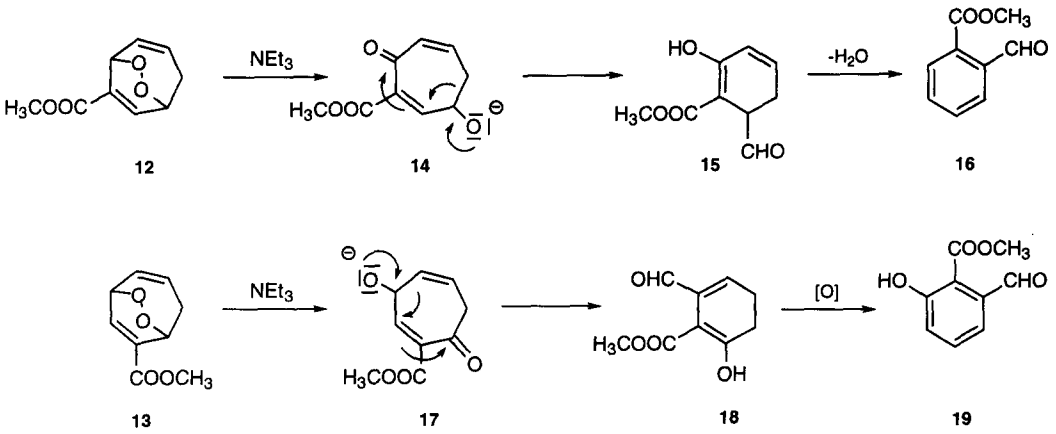
transformation and to test the generality of this reaction we have synthesized several bicyclic seven membered ring endoperoxides[6] different position substituted and studied their base-catalyzed transformation.

Results and Discussion

The first set of endoperoxides studied were bridgehead substituted bicyclic endoperoxides **9** and **10**. Replacement of one of the bridgehead protons by any substituent should force the base to attack the other bridgehead proton. To our surprise, the ester **10** polymerized upon treatment with triethylamine whereas the acetyl compound **9** underwent an unusual rearrangement to give aromatic 1,2-dicarbonyl compound **11** (Scheme 3). Recent studies on oxidation of the carcinogen diethylstilbestrol by peroxidases indicated that 1-(4'-hydroxyphenyl)-propan-1,2-dione **11** was one of the cleavage products.[7]



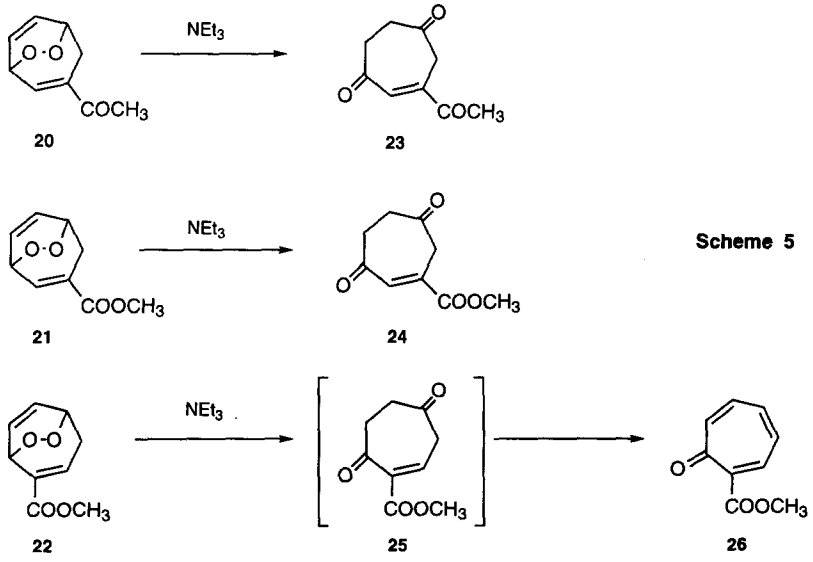
Scheme 3



Scheme 4

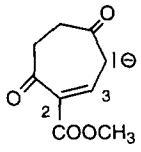
In a second series substituted cycloheptatriene endoperoxides **12** and **13** (substituted in the six-membered ring) were subjected to the triethylamine catalyzed reaction. Again, to our surprise we isolated only ring contraction products **16** and **19** in high yields. Abstraction of the bridgehead proton, which is sterically less hindered by amine catalyst, with concomitant cleavage of the O-O bond might generate the unsaturated keto alkoxides **14** and **17** which could then afford **16** and **19**[8] via retro-aldol cleavage. We assume that the attachment of an electron withdrawing group to the ring activates the C-C double bond which in turn promotes the system to easily undergo retro-aldol reaction as shown in Scheme 4.

In the third series we studied base-catalyzed reactions of the endoperoxides bearing electron withdrawing groups (ester, acetyl) attached to the seven membered ring as in **20**, **21** and **22**. However, we obtained completely different products than was seen in the case of **12** and **13**. Compound **20** and **21**



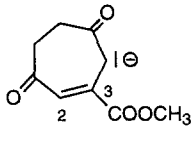
Scheme 5

isomerized to the diketones **23** and **24** instead of the expected hydroxy ketones, whereas the isomer **22** afforded the known tropon derivative **26**.[9] We assume that **22** first underwent similar transformation to give **25** which could easily tautomerize to the corresponding dienol by enolization, followed by elimination of water to provide **26**. AM1 calculations[10] on the systems **23**, **24**, and **25** clearly indicated that compound **25** has the most acidic proton due to the extended conjugation of the carbanion formed with the ester group. Most likely, substituents attached to the C-3 carbon are not capable of stabilizing the carbanion as well as substituents at the C-2 carbon. Results from AM1 calculations show that the conjugated carbanion **25a** has a lower heat of formation than the other isomer **24a** (ΔE = 10.08 kcal/mol) which indicates that **25a** is thermodynamically more stable and can easily undergo enolization. For comparison, we also calculated the heats of formation for the corresponding methyl derivatives **27a** and **28a**, which show similar heats of formations (ΔE = 0.64 kcal/mol) as they have no π-conjugation with the methyl group.



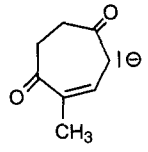
25a

ΔH_F= -188.31 kcal/mol



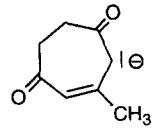
24a

ΔH_F= -179.31 kcal/mol



27a

ΔH_F= -101.30 kcal/mol

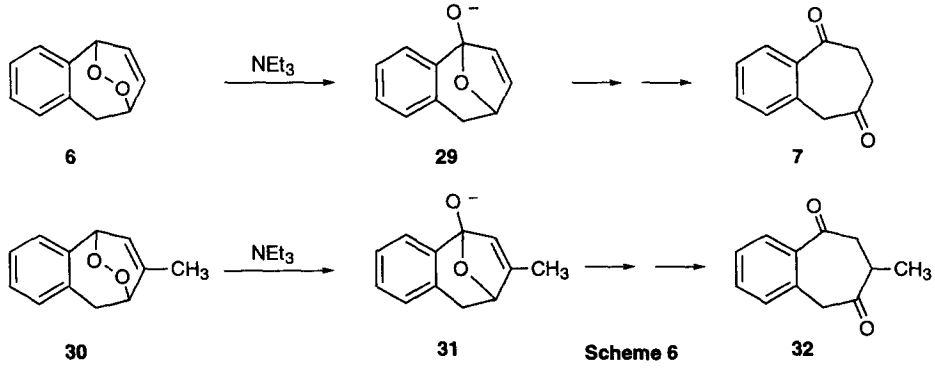


28a

ΔH_F= -100.64 kcal/mol

On the basis of these calculations we assume that diketone **25** might be easily transformed to tropon derivative **26**, where the other compounds **23** and **24** can not. Furthermore, opening of peroxide **22** to the corresponding hydroxyketone followed by elimination of water should also be considered as an alternative mechanism leading to the tropon derivative **26**.

Most recently, our ^{1}H-NMR spectroscopic studies on the base-catalyzed rearrangement of **6** into diketone **7** indicated that **7** was not the primary product. On basis of the characteristic NMR data derived from the intermediate we postulated that endoperoxide **6** was converted to the hemi-acetal which ultimately rearranges to the diketone **7**. We have synthesized the corresponding methyl derivative **30** and followed the rearrangement by ^{1}H- and ^{13}C-NMR and observed that **30** underwent transformation in a similar fashion to the corresponding diketone **32**.



6 **29** **7**

30 **31** **32**

Scheme 6

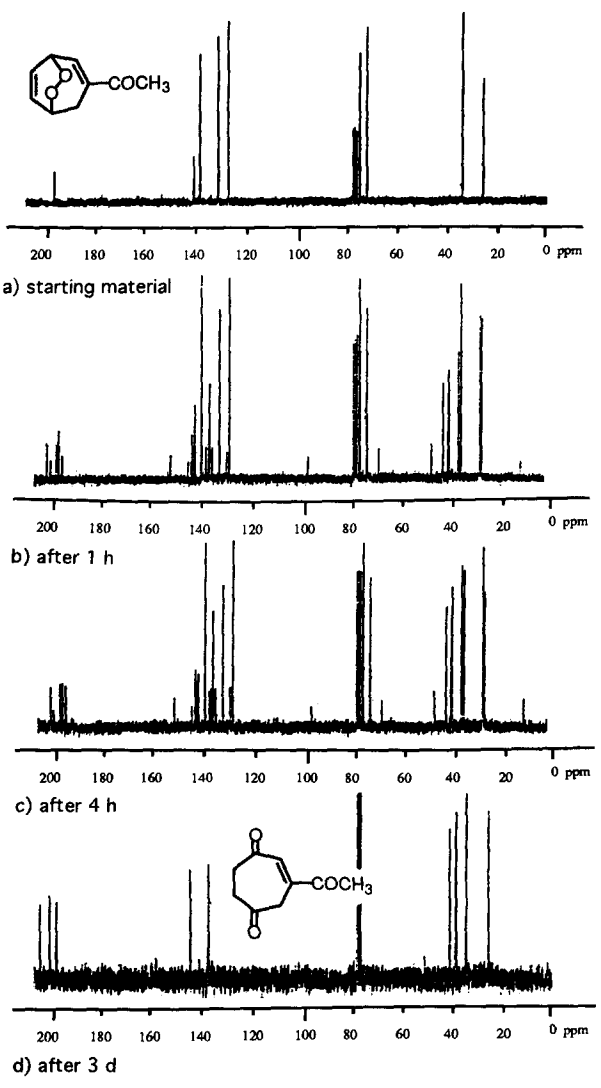
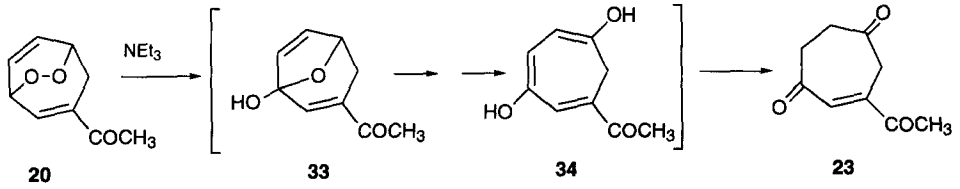


Figure 1. 50 MHz ^{13}C-NMR spectra from the NEt_3-catalyzed reaction of endoperoxide **20** taken at various times.

In order to elucidate the mechanism of this interesting and unusual base-catalyzed rearrangement of the endoperoxides **20** and **21**, we have followed the rearrangement of acetyl derivative **20** with ^{13}C-NMR spectroscopy. However, in this case we observed a different intermediate than was expected. As one can see from the ^{13}C-NMR spectra, taken at various intervals, an intermediate was formed, which rearranged smoothly to the diketone **23**. Most notably, the number of signals appearing in the olefinic region increased. The ^{13}C NMR peaks belonging to the intermediate are δ = 204.3, 152.3, 142.1, 138.1, 135.4, 129.1, 96.5 68.0, 26.6 ppm. In the light of this observation we assume that the endoperoxide **20** can be either directly transformed into dienol **34** which slowly tautomerizes to the diketone **23**, or, primarily formed cyclic ether **33** can rearrange rapidly into the dienol **34** as in the case of benzocycloheptatriene systems, the removal of the bridgehead proton and ring opening take place in a concerted fashion.



20 **33** **34** **23**

Scheme 7

Finally, since we were surprised that none of the substituted cycloheptatriene derivatives formed any trace of the expected base-catalyzed ring opening products like **35** or **36**, we decided to evaluate the relative stability of the possible isomers **23**, **35** and **36**. To do this we carried out AM1 calculations.[10] The results of

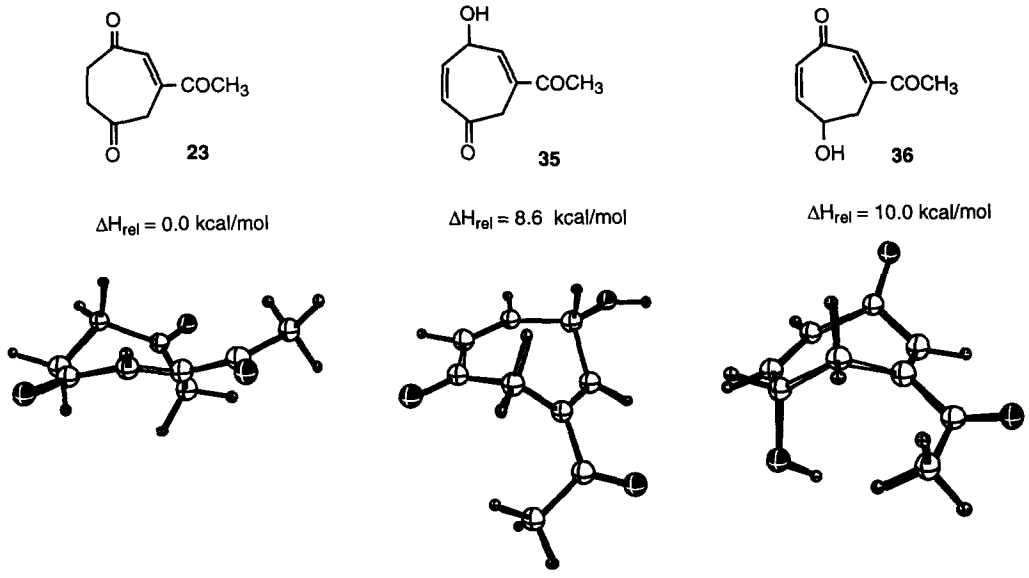


Figure 2. Possible base-catalyzed ring opening products derived from endoperoxides **23** and their AM1 heat of formation energies.

our computational investigation of these isomers indicated that the formed diketone **23** is the thermodynamically most stable by values of 9-10 kcal/mol greater than the isomeric hydroxy ketones **35** and **36**. Therefore, the formation of **23, 24** and **25** rather than the expected hydroxy ketons **35** and **36**, can be explained.

These experiments demonstrate that triethylamine-catalyzed rearrangement of substituted cycloheptatriene endoperoxides is completely dependent on the location of the substituent. If substituents with electron withdrawing ability are attached to the six-membered ring, retro-aldol type condensation reactions primarily occur. This provides a synthetic entry to highly substituted phenol derivatives. On the other hand, endoperoxides bearing substituents on the seven membered ring undergo isomerization to form diketone derivatives. Finally, the behavior of bridgehead substituted endoperoxides is totally dependent on the nature of the substituent. For example, ester **10** polymerizes upon treatment with triethylamine whereas acetyl compound **9** undergoes ring contraction to form a 1,2-dicarbonyl compound.

Experimental

General: Melting points were determined on a Thomas-Hoover capillary melting apparatus. Infrared spectra were obtained from films on NaCl plates for liquid or KBr pellets for solids on a Perkin-Elmer 337 infrared recording spectrometer. ^{1}H- and ^{13}C- NMR spectra were recorded on 200 (50 MHz) Varian spectrometers, and are reported in δ units with $SiMe_4$ as internal standard. All column chromatography was performed on silica gel (60 mesh, Merck).

General Procedure of NEt-catalyzed Rearrangement of Endoperoxides: A solution of the endoperoxide (500 mg) in 10 mL dichloromethane containing triethylamine (100 mg, 1 mmol) was stirred at 0 °C until

complete consumption of the peroxide (monitored by peroxide test with potassium iodide), usually 2-4 h. After evaporation of the solvent, the residue was passed through a small silica-gel column (10 g) eluting with appropriate solvents to remove triethylamine.

NEt_3 Catalyzed Reaction of 1-Acetyl-6,7-dioxabicyclo[3.2.2]nona-3,8-diene (9): Synthesis of 1-(4-hydroxy-phenyl)-1,2-propanedion: 171 mg, 35 %); ^1H NMR (200 MHz, $CDCl_3$) δ 7.95 (br. d, A-part of AB-system, J= 6.86 Hz, 2H), 6.80 (br. d, B-part of AB-system, J= 6.86 Hz, 2H), 5.50 (br. s, 1H, -OH) 2.50 (s, 3H, $COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.19, 190.22, 162.16, 133.85, 125.15, 117.96, 27.14; IR (NaCl cm^{-1}) 3210, 3012, 2980, 2850, 1716, 1680, 1430, 1390, 1245.

NEt_3 Catalyzed Reaction of Methyl-6,7-dioxabicyclo[3.2.2]nona-2,8-diene-8-carboxylate (12) : Methyl 2-formylbenzoate (16): (320 mg, 64 %); ^1H NMR (200 MHz, $CDCl_3$) δ 10.62 (s, aldehyde, 1H), 7.95 (m, aromatic, 2H, H_3 and H_6), 7.65 (m, aromatic, 2H, H_4 and H_5), 3.96 (s, 3H, $COOCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 192.16, 165.55, 137.66, 136.22, 133.58, 132.44, 130.50, 128.47, 52.56.

NEt_3 Catalyzed Reaction of Methyl-6,7-dioxabicyclo[3.2.2]nona-2,8-diene-9-carboxylate (13): Methyl 2-hydroxy-6-formyl benzoate 19. (160 mg 32 %); ^1H NMR (200 MHz, $CDCl_3$) δ 10.9 (br.s, 1H, -OH) 10.47 (s, aldehyde, 1H), 7.56 (br. t, J=7.7 Hz, aromatic, 1H, H_4), 7.30 (dd. J=7.7 and 1.2 Hz, aromatic 1H, H_3 or H_5), 7..20 (dd, J=7.7 and 1.2 Hz, aromatic 1H, H_3 or H_5), 4.0 (s, 3H, $COOCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 192.16, 162.23, 140.94, 140.41, 140.06, 138.16, 124.72, 121.40, 52.14. IR (NaCl cm^{-1}) 3200, 2980, 1700-1690, 1580.

NEt_3 Catalyzed Reaction of 3-Acetyl-6,7-dioxabicyclo[3.2.2]nona-2,8-diene (20) : Synthesis of **3-Acetyl-2-cyclohepten-1.5-dion (23):** (colorless liquid, 480 mg, 96%); ^1H NMR (200 MHz, $CDCl_3$) δ 6.80 (s, olefinic 1H, H_2), 3.80 (s, methylenic 2H, H_3), 2.98 (A-part of AB-system, methylenic 2H, H_6 or H_7) 2.60 (B-part of AB-system, methylenic 2H, H_6 or H_7), 2.40 (s, 3H, $COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.31, 200.14, 198.46, 144.12, 136.86, 41.22, 38.53, 34.61, 24.82; IR (NaCl cm^{-1}) 2980, 2910, 1705, 1660. Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07; Found: C, 65.30; H, 6.25.

NEt_3 Catalyzed Reaction of Methyl 6,7-dioxabicyclo[3.2.2]nona-2,8-diene-3-carboxylate (21): Synthesis of **Methyl 1,5-dion-2-cycloheptene-3-carboxylate (24)**: (colorless liquid, 470 mg, 94%); ^1H NMR (200 MHz, $CDCl_3$) δ 7.10 (s, olefinic 1H, H_2), 3.87 (s, methylenic 2H, H_3), 3.80 (s, 3H, $COOCH_3$), 2.95 (A-part of AB-system, methylenic 2H, H_6 or H_7) 2.63 (B-part of AB-system, methylenic 2H, H_6 or H_7), ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.18, 198.23, 164.95, 142.86, 137.72, 52.14, 42.33, 39.85, 34.15; IR (NaCl cm^{-1}) 2980, 2910, 1705, 1660. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.49; Found: C, 59.00; H, 5.23.

NEt_3 Catalyzed Reaction of Methyl 6,7-dioxabicyclo[3.2.2]nona-2,8-diene-2-carboxylate (22): Synthesis of **Methyl 7-oxo-1,3,5-cycloheptatriene-1-carboxylate (26) :** (90 mg, 18%); ^1H NMR (200 MHz, $CDCl_3$) δ 7.85 (br. d, olefinic 1H, H_2 or H_6), 7.96 (br. d, olefinic 1H, H_2 or H_6), 7.0-7.3 (m, olefinic, 3H, H_3 H_4, and H_5) 3.95 (s, 3H, $COOCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 187.43, 148.12, 142.26, 139.08, 136.55, 125.62, 125.40, 52.78, IR (NaCl cm^{-1}) 2980, 2910, 1705, 1660.

3-Methyl-3-5H-benzocycloheptene (38): A stirred solution of 3-bromo-5H-benzocycloheptene (**37**) (3.0 g, 13.6 mmol) in dry THF (100 mL) was cooled to -70 °C under a nitrogen atmosphere and treated dropwise with a solution of butyllithium (11 mL, 16.3 mmol) in hexane. After the addition was complete, stirring was continued for 3 h. CH_3I (2.32 g, 16.3 mmol) was then added at -70 °C and the solution stirred for an additional 1 h. The reaction mixture was allowed to warm to room temperature and 15 mL water was added slowly. The THF was removed under reduced pressure and 50 mL water was added. The solution was then extracted three

times with n-hexane. The combined organic layers were dried and evaporated. The oily residue was subjected to column chromatography (100g, silica gel). Elution with hexane afforded **38** ; (colorless liquid, 1.5 g 70%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.14-7.40 (m, aromatic, 4H), 7.05 (d, A-part of AB-system, 1H, olefinic), 6.40 (d, B-part of AB-system, 1H, olefinic), 5.52 (t, 1H, olefinic), 3.0 (d, 2H, methylenic), 1.91 (s, 3H, Me).

Photooxygenation of 38: To a magnetically stirred solution of **38** (3.0 g, 19.2 mmol) in 400 mL CCl_4 was added 50 mg tetraphenylporpyrine (TPP) as a sensitizer. The solution was irradiated with a projector lamp (150 watt) at room temperature while continuously passing a slow stream of dry oxygen gas. The progress of the photooxygenation was monitored by ^{1}H-NMR until total consumption of the starting material. After 24 h the reaction was completed. The solvent was rotoevaporated (15 mm Hg, rt) and the residue was chromatographed on silica gel (250 g) eluting with ethyl acetate/hexane (3:97).

1. Fraction : 80 mg naphthalene; 2. Fraction 350 mg 2-methylnaphtaldehyde; 3. Fraction 1.5 g of endoperoxide **30** and 2-methylnaphtaldehyde (2:1); 4. Fraction : 400 mg (12%) of pure endoperoxide **30** (colorless liquid); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.05-7.28 (m, 4H, aromatic), 6.42 (br d, J=7.4 Hz, 1H, olefinic), 5.21 (d, J=7.4 Hz, 1H, bridgehead), 4.77 (m, 1H, bridgehead), 3.61 (dd, A-part of AB-system, J= 18.0, 4.0 Hz, 1H, methylenic), 3.18 (dd, B-part of AB-system, J= 18.0, 2.7 Hz, 1H, methylenic), 1.91 (s, 3H, Me); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.48, 136.27 (2x), 131.37, 128.54, 127.23, 126.59, 126.30, 80.73, 80.37, 37.12, 20.27; IR (NaCl cm^{-1}) 3000-3020, 1490, 1410, 1185. Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.42; Found: C, 76.01; H, 6.60.

NEt_3 Catalyzed Reaction of 2,3-Benzo-6,7-dioxa-9-methyl-bicyclo[3.2.2]nona-2.8-diene (30): Synthesis of 3-**Methyl-6,7-Benzo-cycloheptene-1.4-dion (32)**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (dd, aromatic, 1H), 7.52 (t, aromatic, 1H), 7.40 (t, aromatic, 1H), 7.24 (d, aromatic, 1H), 3.86-4.19 (AB-system, J= 4.55 Hz, 2H, methylenic), 2.94-3.16 (AB-system J=16.8 Hz, 2H, methylenic), 3.05 (m, 1H), 1.18 (d, J=8 Hz, $-CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.08, 200.51, 136.23, 134.52, 134.20, 131.36, 130.61, 129.65, 51.43, 47.38, 40.30, 16.66; IR (KBr, cm^{-1}) 3000-3020, 1730, 1680, 1275; Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.42; Found: C, 75.77; H, 6.31.

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