# SYNTHESIS OF POLYCYCLIC 1,2-DIOXANES FROM ENDOPEROXIDES

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*Abstract-* 1,4-Diphenylcyclohex-2-ene 1,4-endoperoxide (**7**) on catalysis with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in $CH_2Cl_2$ at -78°C reacted partially with 1,4-diphenylcyclopenta-1,3-diene (**5**) to give 3a,5a,6,7,9a,9b-hexahydro-2,5a,8,9b-tetraphenyl-1*H*-4,5-dioxacyclopenta[*a*]naphthalene (**8**) in 7.5% yield. Similar reaction of 1-phenylcyclohex-2-ene 1,4-endoperoxide (**9**) with 1-phenylcyclohexa-1,3-diene (**10**) afforded three 1,2-dioxanes in a combined yield of 45%, one of which was identified as 1,2,4a,6a,7,8,10a,10b-octahydro-3,9-diphenyl-5,6-dioxaphenanthrene (**11**). The TMSOTf-catalysed reaction of 1,4-dihydro-1,4-dimethylnaphthalene 1,4-endoperoxide (**12**) with 1,4-diphenylcyclopenta-1,3-diene (**5**), benzofuran (**14**) and 1,1-diphenylethylene (**16**) gave the *endo cis*-fused tricyclic 1,2-dioxanes, (**13**), (**15**), and the *cis*-fused bicyclic 1,2-dioxane (**17**) as single products in yields of 46, 81, and 72% respectively. The structures of **8**, **11**, **13**, **15** and **17** were elucidated by X-Ray analysis.

## INTRODUCTION

Apart from applications as a chemical source of singlet oxygen, endoperoxides are rarely used as reagents in organic chemistry.[1] Notable exceptions are their reactions with aldehydes and ketones which have been exploited for preparing a great variety of 1,2,4-trioxanes,[2] some of which display powerful antimalarial activity.[3] A classic example[4] is the synthesis of the *cis*-fused cyclopenteno-1,2,4-trioxane (**4**) by the acid-catalysed accretion of cyclopentanone (**3**) to 1,4-diphenylcyclopent-2-ene 1,4-endoperoxide (**1**) (Scheme 1). It is believed that Lewis acid ($E^+$) first attacks the peroxide bond to create the peroxy-allylic cation (**2**) which then combines with **3** in the expected electronic sense. Because **1** is symmetrical, the enantiomer of **4** is obtained as well, thereby affording a racemic mixture. We recently discovered[5] that **1** reacts analogously with olefins to give the corresponding 1,2-dioxanes, a potentially interesting class of heterocycles which includes several biologically active members.[6] Typically, 1,4-diphenylcyclopenta-1,3-diene (**5**) and **1** on catalysis with trimethylsilyl trifluoromethansulfonate (TMSOTf) in $CH_2Cl_2$ at -78°C combine in a regio- and stereospecific manner to give the *endo-cis* tricyclic 1,2-dioxane (**6**) (Scheme 2).

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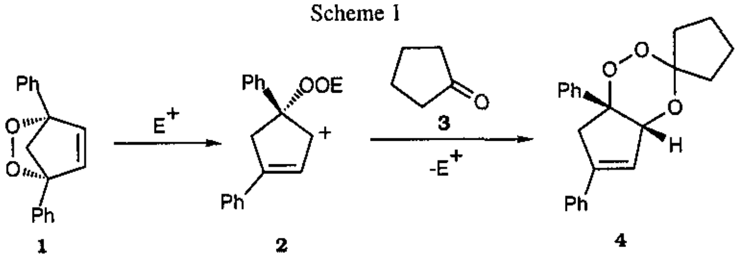
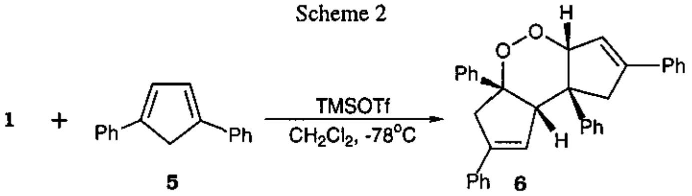
Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

Scheme 1



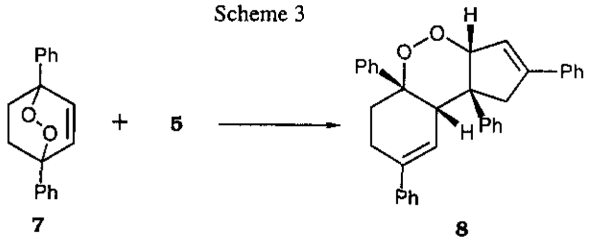
Scheme 2



## RESULTS AND DISCUSSION

We now describe experiments with other endoperoxides that explore the scope of this unusual reaction. First, the reaction of 1,4-diphenylcyclohex-2-ene 1,4-endoperoxide (**7**) with **5** was assayed.[7] Catalysis with TMSOTf in $CH_2Cl_2$ at -78°C for 1 h followed by neutralization with $Et_3N$ and flash chromatography gave a single product (**8**), the higher homologue of **6**, possessing the central 1,2-dioxane ring fused in the same *cis* fashion to the two outer rings (Scheme 3). Despite several attempts, conversions were never complete. Yields were usually 7.5% and could not be improved by varying the temperature or the amount of TMSOTf used.

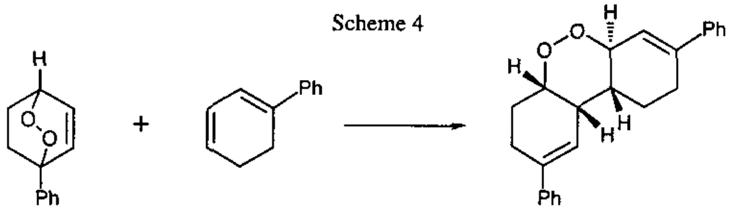
Scheme 3



Surprisingly, repeating the experiment with 1,4-diphenylcyclohexa-1,3-diene instead of **5** failed totally; no products were observed. Next, the reaction of 1-phenylcyclohex-2-ene 1,4-endoperoxide (**9**) with 1-phenylcyclohexa-1,3-diene (**10**) was tried (Scheme 4). Again, only 50% conversion could be achieved at best. Examination of the crude reaction mixture by NMR spectroscopy revealed that three isomeric 1,2-dioxanes had formed in 45% yield. Unfortunately, their separation by chromatography was only partially successful. Just one, the *trans*-fused isomer (**11**), was isolated in 5% yield .

A second series of experiments was undertaken with 1,4-dihydro-1,4-dimethylnaphthalene-1,4-endoperoxide (**12**). The results were far more promising. The TMSOTf-catalysed reactions of **12** with 1,4-diphenylcyclopenta-1,3-diene (**5**), benzofuran (**14**) and 1,1-diphenylethylene (**16**) in $CH_2Cl_2$ at -78°C proceeded efficiently and with complete conversion (Scheme 5). The 1,2-dioxanes (**13**), (**15**), and (**17**) were formed as single products and isolated in yields of 46%, 81%, and 72% respectively.[11]

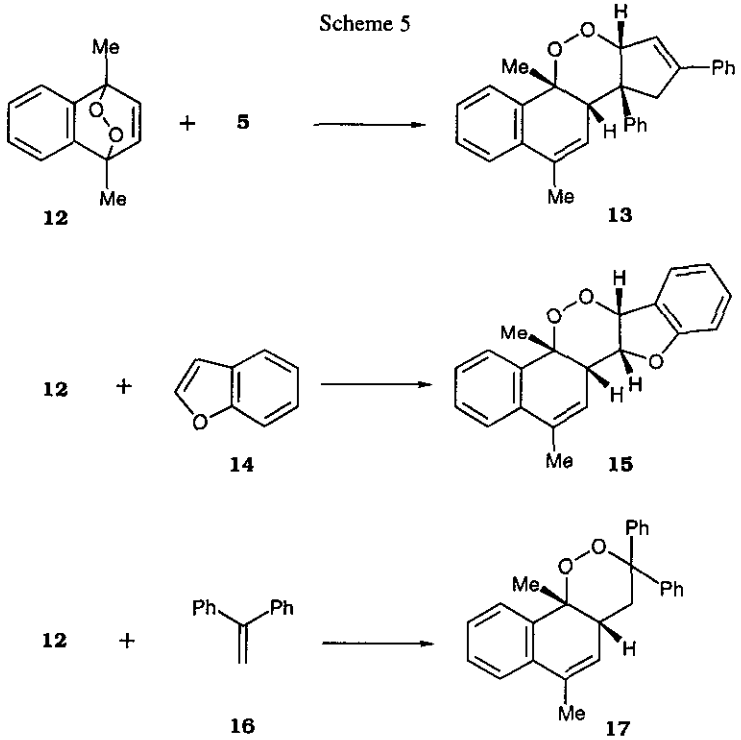
Scheme 4



**9** **10** **11**

The 1,2-dioxanes (**8**), (**11**), (**13**), (**15**), and (**17**)[12] furnished single crystals suitable for X-Ray analysis thereby enabling their constitution and relative configurations to be determined.[13] As an illustration of the two types of dioxane so obtained, the crystal structures of **8** and **15** are shown (Figure). The cyclohexene and cyclopentene rings in **8** exist as envelope and nearly planar conformations respectively. Both rings lie *endo* to each other and are *cis*-fused to the central 1,2-dioxane ring which adopts a twist-boat conformation characterized by a pseudo-$C_2$ axis passing through the middle of the peroxide bond ($\Delta C_2$(O1-O2) = 0.021).[16] The relative configuration of **15** is the same as that of **8**. The dihydronaphthalene and benzofuran moieties are attached *cis* to the same side of the dioxane ring which is constrained as a deformed chair conformation ($\Delta C_2$(O1-O2) = 0.009)[16] bearing the methyl and benzyl substituents in equatorial positions.

Scheme 5



**12** **13** **14** **15** **16** **17**

Regardless of the differences in yields, which are clearly superior for **12**, all endoperoxides couple with the olefins regiospecifically. Moreover, except for the mono-substituted peroxide (**9**), all reactions are diastereospecific. The stereochemical course may be rationalized in terms of the electrophilic behavior of the intermediate trimethylsilyl peroxy cations. The coupling of the enantiomeric cation (**18**), obtained by addition of TMSOTf to **12**, with 1,4-diphenylcyclopenta-1,3-diene (**5**) serves as an example (Scheme 6).

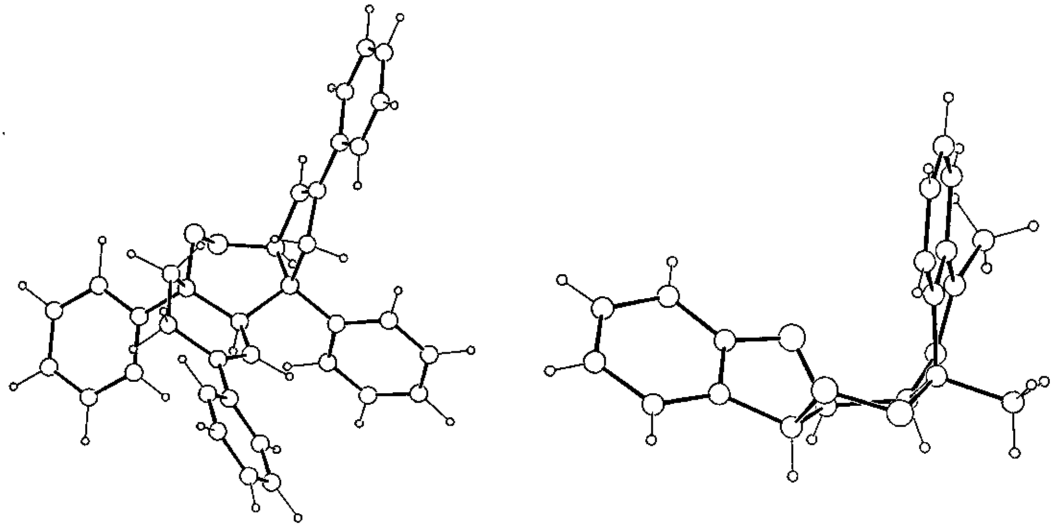
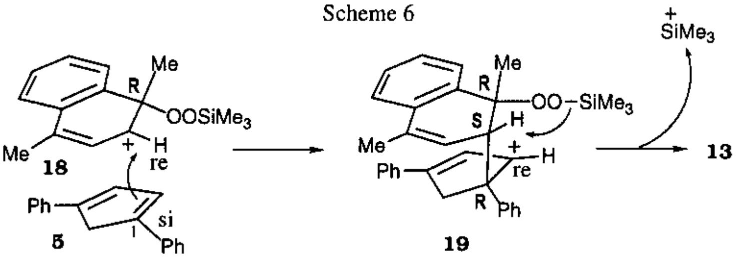


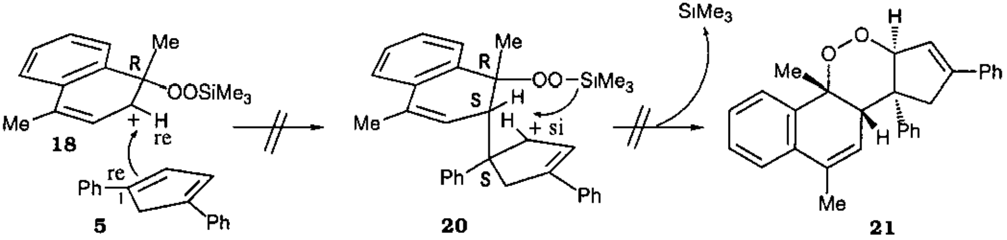
Figure. Perspective drawings of the crystal structures of 1,2-dioxanes (**8**) and (**15**).

The key step is the creation of the carbon-carbon bond between the cationic center of **18** and the C1 atom of **5** on their *re* and *si* faces respectively. The resulting allylic cation (**19**) subsequently undergoes attack on its *re* face by the contiguous peroxide group, eliminating at the same time the trimethylsilyl cation, to give **13**. Thus, the newly formed 1,2-dioxane ring is *cis*-fused both to the naphthalene entity from whence it came and to the cyclo-olefinic partner. The overall process is reminiscent of the Diels-Alder reaction in that an *endo-cis* arrangement of reactants is followed. The alternative, apparently less congested, arrangement involving attack by the *re* face of **5** on **18**, leading successively to the cation (**20**) and *exo-cis* product (**21**), is not observed (Scheme 7).

Scheme 6



Scheme 7



It is noteworthy that dioxane (**11**) retains the configuration conferred by the first step of the reaction of **9** with **10**, namely the *cis*-disposition of the peroxide-derived cyclohexene and dioxane rings. However, stereochemical control is lost in the second step as evidenced by the *trans*-fused third ring.

## CONCLUSIONS

The present results demonstrate a new, general reaction of symmetrical endoperoxides with olefins that provides a further method for synthesizing polycyclic 1,2-dioxanes.[17] The reaction is subject to regio- and diastereoslective control and is characterized by *endo-cis* stereochemistry. A logical extension of the above-mentioned mechanistic principles is to exploit 1,2-dioxetanes and allylic hydroperoxides for preparing 1,2-dioxanes. Such applications as well as studies on the chemical and biological properties of polycyclic 1,2-dioxanes will be reported in due course.

## ACKNOWLEDGMENTS

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7. Endoperoxides (**7**), (**9**) and (**12**) were prepared by the *meso*-tetraphenylporphyrin-sensitized photooxygenation of 1,4-diphenyl- and 1-phenylcyclohexa-1,3-diene,[8,9] and 1,4-dimethylnaphthalene in $CCl_4/CH_2Cl_2$ (9:1) for 1-4 h under irradiation by a tungsten filament lamp (500 Watt). After evaporating the solvent, the crude endoperoxide was used directly. Typically, the endoperoxide (3 mmol) and olefin (6 mmol) were dissolved in $CH_2Cl_2$ (100 mL) under Ar. TMSOTf (1.5 mmol) was added to the solution and stirred at -78°C for 1 h. The resulting mixture was quenched with $Et_3N$ (1.5 mmol), washed ($H_2O$), dried ($Na_2SO_4$) and evaporated. Dioxane product was purified by flash chromatography[10] over silica gel 60 (0.040-0.063 mm, Merck) or by crystallization.
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11. The lower yield of **13** was due to poor solubility in the eluent. Dioxane (**17**) was crystallized from the reaction mixture without recourse to chromatography.
12. 1,2-Dioxanes (**8**), (**11**), (**13**), (**15**), and (**17**) are racemates and, after recrystallization (solvent), gave mp of 220-224°C (i-$Pr_2O$), 164-167°C ($CH_2Cl_2/Et_2O$), 166-167°C ($CH_2Cl_2$/i-PrOH), 157-161°C ($CH_2Cl_2$/hexane), and 139-141°C (hexane), respectively. All compounds are new and gave acceptable elemental analyses.
13. *Crystallographic data*: Crystals of **8** were grown at rt from a solution in *i*-$Pr_2O$. A colorless crystal (0.03 x 0.20 x 0.28 mm) was measured on a Nonius CAD4 diffractometer with graphite monochromated MoK$\alpha$ radiation ($\lambda = 0.71069$ Å). $C_{35}H_{30}O_2$, Mw 482.6, monoclinic, $P2_1/n$, a = 8.770(2), b = 18.091(4), c = 16.111 Å, $\beta = 96.58(3)°$, V = 2539(1) $Å^3$, Z = 4, $D_x = 1.26$ $g.cm^{-3}$, Fooo = 1024, $\mu(MoK\alpha) = 0.071$ $mm^{-1}$; R = $\omega$R = 0.092 ($\omega = 1$) for 1647 observed reflections ($|Fo| > 4\sigma(Fo)$).
14. Crystals of **15** were grown from a solution in $CH_2Cl_2$/hexane. A colorless crystal (0.22 x 0.25 x 0.30 mm) was measured as above with CuK$\alpha$ radiation, ($\lambda = 1.5418$ Å). $C_{20}H_{18}O_3$, Mw 306.4, triclinic, P1, a = 6.852(1), b = 9.1799(6), c = 13.609(1) Å, $\alpha = 109.275(6)$, $\beta = 90.275(5)$, $\gamma = 100.708(5)°$, V = 791.89(7) $Å^3$, Z = 2, $D_x = 1.28$ $g.cm^{-3}$, Fooo = 324, $\mu(CuK\alpha) = 0.650$ $mm^{-1}$; R = 0.046, $\omega$R = 0.044 ($\omega = 1/\sigma^2(Fo)$) for 1940 observed reflections ($|Fo| > 4\sigma(Fo)$). Both structures were solved by direct methods (Multan87)[14] and refined by full-matrix least squares (XTAL).[15] All coordinates of H atoms were calculated. Data have been deposited with the Cambridge Crystallographic Data Centre.
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