Stereospecific Syntheses of the Three Trioxides of 1,3,5-Cycloheptatriene via the Endoperoxide–Diepoxide Rearrangement[1]

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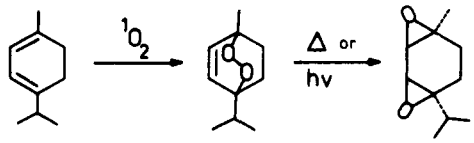
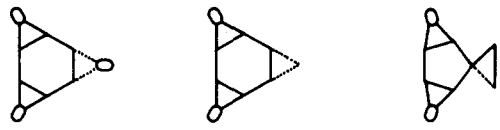
Abstract: The syn,syn (**3a**), syn,anti (**3b**), and anti,anti (**3c**) trioxides have been prepared from 1,3,5-cycloheptatriene via stereospecific syntheses. Singlet oxygenation (i), endoperoxide rearrangement (ii), and peracid epoxidation (iii) were engaged as synthetic tools, achieving the desired stereochemistry through appropriate sequencing of the above reactions. The [2 + 4] endoperoxide **1a**, monoepoxide **1b**, and [2 + 6] endoperoxide **1c** of cycloheptatriene served as respective starting points in the stereospecific design of trioxides **3a**, **3b**, and **3c**.

Our fascination with the intriguing endoperoxide–diepoxide rearrangement (eq 1), illustrated for ascaridole,[3] was expressed some time ago in a review[4] dealing with the synthetic utilization of cyclic peroxides. Since the endoperoxides are readily prepared by [2 + 4] cycloaddition of singlet oxygen to conjugated cyclodienes, with a minimum of synthetic effort complex oxygen functionalities are introduced stereospecifically in readily available hydrocarbon substrates.



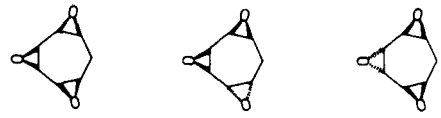
(eq. 1)

It is, therefore, not surprising that the preparatively valuable endoperoxide–diepoxide transformation has been employed in a number of interesting synthetic problems, facilitating the design of complex organic structures. For example, in this elegant fashion the syn,anti trioxide of benzene was prepared



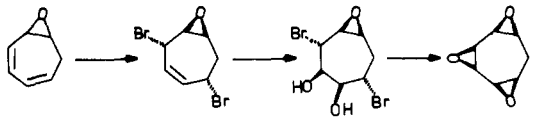
independently by Vogel[5] and by Berchthold,[6] both utilizing benzene oxide or oxepin as substrate in eq 1. More recently, work from our own group has illustrated[7a] that the then still missing norcaradiene *syn,anti*-diepoxide could be readily prepared via the synthetic sequence of eq 1 starting from cycloheptatriene. Similarly, the preparation of the interesting syn diepoxide derived from spirocyclopentadiene could be realized[8] with the help of this synthetic concept.

It was with this motivation that we commenced the preparation of the three isomeric trioxides of 1,3,5-cycloheptatriene,



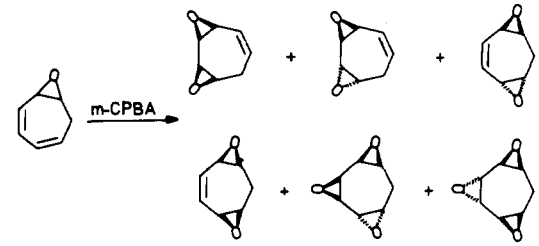
syn,syn syn,anti anti,anti

utilizing the endoperoxide–diepoxide rearrangement (eq 1) to fix stereospecifically the epoxide rings. A preliminary report on our results has been made;[9] however, prior to our efforts on this synthetic problem, Prinzbach[10] had prepared the syn,syn trioxides via the classical route shown in eq 2, affording the



(eq. 2)

syn,syn isomer. An X-ray determination confirmed its structure. Moreover, the syn,anti and anti,anti trioxides were claimed also by Prinzbach[10] as a complex mixture in the exhaustive epoxidation of cycloheptatriene oxide with *m*-chloroperbenzoic acid (eq 3). Unfortunately, no structure confirmation could be made because the complex mixture of trioxides and dioxides could not be separated even by gas chromatography. Herein we make a full account of our work on the stereospecific design of the three trioxide isomers of cycloheptatriene, utilizing (i) singlet oxygenation, (ii) endoperoxide rearrangement, and (iii) epoxidation as the basic synthetic tools and permuting the order of these transformations.



(eq. 3)

Results and Discussion

For convenience and reference an overview of the various stereospecific routes for the synthesis of the three trioxides of cycloheptatriene is given in Scheme I. It is clearly evident from the scheme how through proper choice of the substrates **1**, all conveniently derived from cycloheptatriene, and judicious permutation of the three essential transformations, i.e., singlet oxygenation (i), endoperoxide rearrangement (ii), and epoxidation (iii), the three possible stereoisomeric trioxides **3** could be prepared with relatively little synthetic effort, considering the complexity of these interesting molecules. Let us first discuss the syn,syn trioxide **3a**.

Syn,Syn Trioxide 3a. As Scheme I reveals, two synthetic pathways have been accomplished. In the **1a** → **2a** → **3a** route, fortunately, the precursor ene dioxide **2a** was available in 11% yield via the thermal endoperoxide rearrangement[11] of the tropilidene-derived [2 + 4] cycloadduct **1a**, formed in 42% yield in the singlet oxygenation of cycloheptatriene.[7] Therefore, only epoxidation of the precursor **2a** remained to accomplish our goal. Inspection of Dreiding models exhibited the unique conformational feature that peracid attack should be least encumbered from the syn face. Indeed, treatment of **2a** with *m*-chloroperbenzoic acid (*m*-CPBA) gave exclusively the desired syn,syn trioxide **3a** in 42% yield. The spectral data in Table I corroborate the claimed syn,syn structure, especially the ^{13}C NMR. The fact that the proton-decoupled spectrum gave only three distinct epoxide and one methylene carbon

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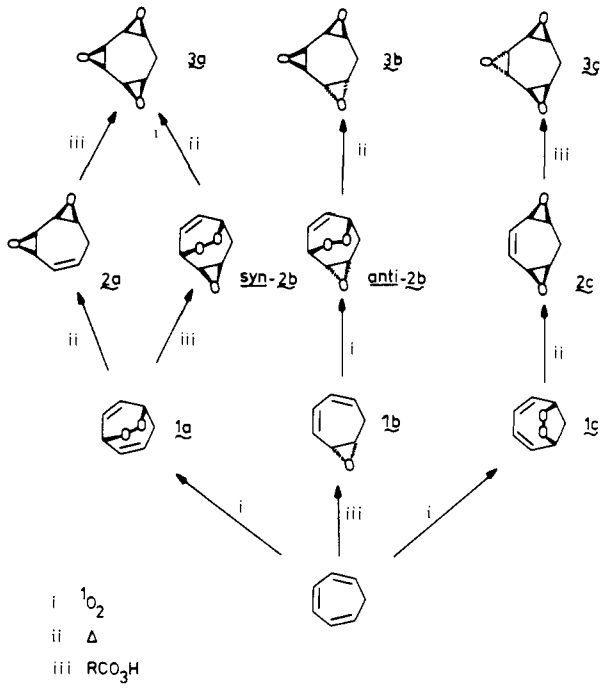
Table I. Spectral Data of Trioxides **3**

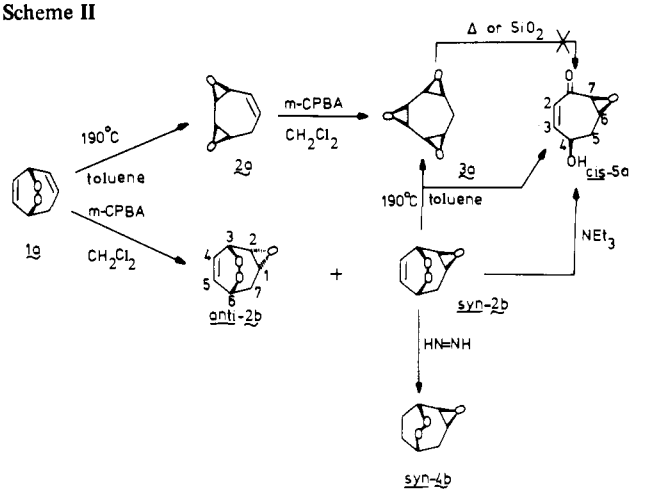
trioxide	^{1}H NMR ($CDCl_3$, Me_4Si) type[b]	no.	δ, ppm	pattern	J, Hz[c]	^{13}C NMR ($CDCl_3$)[a] type	δ, ppm	IR ($CHCl_3$) ν, cm^{-1}
syn,syn-**3a**	7	1	1.7-2.1	m	$J_{23} \leq 1.5$	7	28.19	3030
	7′	1	2.4-2.8	m	$J_{17} = 8.0$	3,4	50.56	3000
	1,2,5,6	4	2.9-3.4	m	$J_{17'} = 6.0$	1,6	52.61	1440
	3,4	2	3.55	br s	$J_{77'} = 14$	2,5	53.11	980
								940
								880
syn,anti-**3b**	7	1	1.6-2.0	m		7	27.36	3040
	1,2,3,4		2.4-3.4	m		3	50.35	3020
	5,6,7′	7				4	50.39	1455
						6	50.70	1010
						1	51.39	915
						5	52.83	850
						2	53.19	840
anti,anti-**3c**	7	1	0.7-1.25	m	$J_{17} = 8.19$	7	32.25	3000[d]
	1,2,3,4		2.45-3.25	m	$J_{17'} = 5.00$	3,4	50.61	2960
	5,6,7′	7			$J_{77'} = 13.50$	1,6	51.86	2930
						2,5	52.29	2890
								1452
								1435
								945
								855

[a] We thank Dr. R. Obenauf (JEOL, New Jersey) and Dr. D. Scheutzow (University of Würzburg) for running these spectra for us. [b] H_7 is endo and $H_{7'}$ is exo. [c] J values of ref 10 were used for *syn,syn*-**3a**. [d] CCl_4.

Scheme I



Scheme II



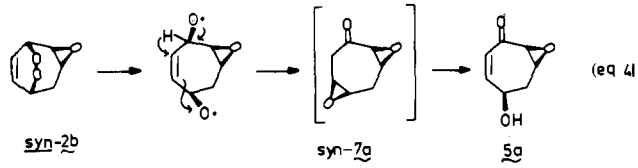
resonances implies a symmetrical molecule. Thus, epoxidation must have occurred from the syn rather than anti side. The off-resonance spectrum further confirms that the three epoxide carbons are doublets and the methylene carbon a triplet.

In the second route, i.e., **1a** → *syn*-**2b** → **3a**, also the endoperoxide **1a** served as starting point, but now the order of transformations was reversed by first conducting the epoxidation and subsequently the endoperoxide rearrangement (Scheme I). The epoxidation of endoperoxide **1a** was sluggish, requiring excess *m*-chloroperbenzoic acid in refluxing CH_2Cl_2 for 36 h. After silica gel chromatography two epoxy endoperoxides were isolated in 11 (first eluate) and 35% (second eluate) yields to which respectively the *anti*-**2b** and *syn*-**2b** structures (Scheme II) were assigned on the basis of their spectral data (Figure 1). The *anti*-**2b** isomer, obtained as a minor product in the epoxidation of endoperoxide **1a**, is identical with that obtained in the singlet oxygenation of cycloheptatriene oxide (**1b**); cf. Scheme I. Therefore, discussion of the *anti*-**2b** isomer is deferred until presentation of the trioxide *syn,anti*-**3b** results (Scheme III).

Chemical characterization of the *syn*-**2b** isomer consisted of diimide reduction in CH_2Cl_2[12] affording the saturated epoxy endoperoxide *syn*-**4b** (Scheme II) in 72% yield. This waxy solid was purified by sublimation, mp 113 °C (correct combustion analysis for the $C_7H_{10}O_3$ elemental composition) and ^{1}H NMR and IR spectral data which are consistent with the proposed structure. Furthermore, isomerization by triethylamine[13] in CH_2Cl_2 at room temperature (ca. 30 °C) led to the unknown *cis*-**5a** in 63% yield (Scheme II). Silica gel chromatography and recrystallization from Et_2O, mp 50-52 °C (correct combustion analysis for the $C_7H_8O_3$ elemental composition), gave the pure material. The IR and ^{1}H NMR spectral data substantiate the structure assignment. In the latter extensive double resonance experiments were particularly conclusive for the elucidation of its stereochemistry. For example, the small $J_{45} = 2.7$ Hz coupling implies a *cis*-4-hydroxyenone structure, as corroborated by Dreiding models.

The thermolysis of the epoxy endoperoxide *syn*-**2b** led to the

expected syn,syn trioxide **3a** in 39% yield, which was identical with the material obtained in the **1a** → **2a** → **3a** route, but heating in toluene at 190 °C for 1 h was essential. Unfortunately, at these high temperatures large amounts of undefined decomposition products (tars) are formed. However, on silica gel chromatography ca. 10% of the *cis*-4-hydroxy-2-enone **5a** could be isolated, which was identical with the sample obtained in the triethylamine isomerization of the endoperoxide *syn*-**2b**. Control experiments revealed that the syn,syn trioxide **3a** was stable to the thermolysis and the silica gel chromatography conditions, indicating that *cis*-**5a** is not a secondary product of *syn,syn*-**3a**. We suspect that the *cis*-**5a** is derived from the syn keto diepoxide **7a** (eq 4) during the thermolysis of *syn*-**2b**.



(eq 4)

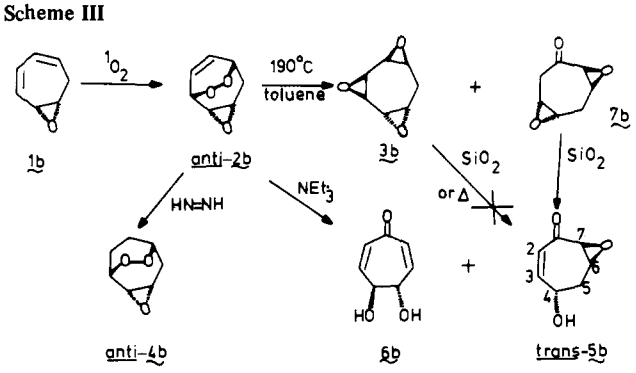
In fact, such α-epoxy ketones as **7a** are expected to be thermally labile at such high temperatures.[14] Additional evidence for this supposition is derived from the thermolysis of the *anti*-**2b** epoxy endoperoxide, in which the anti keto diepoxide **7b** (Scheme III) could be observed in the ^{1}H NMR of the crude thermolysate mixture. The details are deferred to the following section.

Syn,Anti Trioxide 3b. The precursor to the *syn,anti*-**3b** trioxide was the *anti*-**2b** epoxy endoperoxide (Scheme I), which as already mentioned was obtained as a minor product in the epoxidation of the tropilidene-derived endoperoxide **1a** (Scheme II). For our preparative purposes we decided to exploit the singlet oxygenation of cycloheptatriene oxide (**1b**) as starting point, especially since the latter is readily available through peracetic acid epoxidation of cycloheptatriene.[15] Indeed, TPP-photosensitized singlet oxygenation of **1b** in CCl_4 at 0 °C gave the expected *anti*-**2b** epoxy endoperoxide (Scheme III) in 68% yield, purified by silica gel chromatography and recrystallization from 1:4 CH_2Cl_2/Et_2O, mp 125–127 °C, colorless plates (correct combustion analysis for the $C_7H_8O_3$ elemental composition). The IR and ^{1}H NMR spectral data (Figure 1) confirm the structure assignment. Again, double resonance experiments were crucial.

In addition, also some chemical transformations (Scheme III) support the claimed structure. For example, diimide reduction of *anti*-**2b** in CH_2Cl_2[12] at 0 °C afforded the saturated epoxy endoperoxide *anti*-**4b** in 90% yield, waxy solid, mp 134–137 °C after sublimation (correct combustion analysis for the $C_7H_{10}O_3$ elemental composition). The IR and ^{1}H NMR spectral data substantiate the claimed structures.

Furthermore, the triethylamine isomerization[13] afforded the trans hydroxy enone **5b** and the trans diol **6b** in 65 and 27% yields, respectively, after silica gel chromatography. As first eluate, eluting with $CHCl_3$ *trans*-**5b** was obtained, colorless needles, mp 35–38 °C from 3:2 ether/*n*-pentane (correct

Scheme III



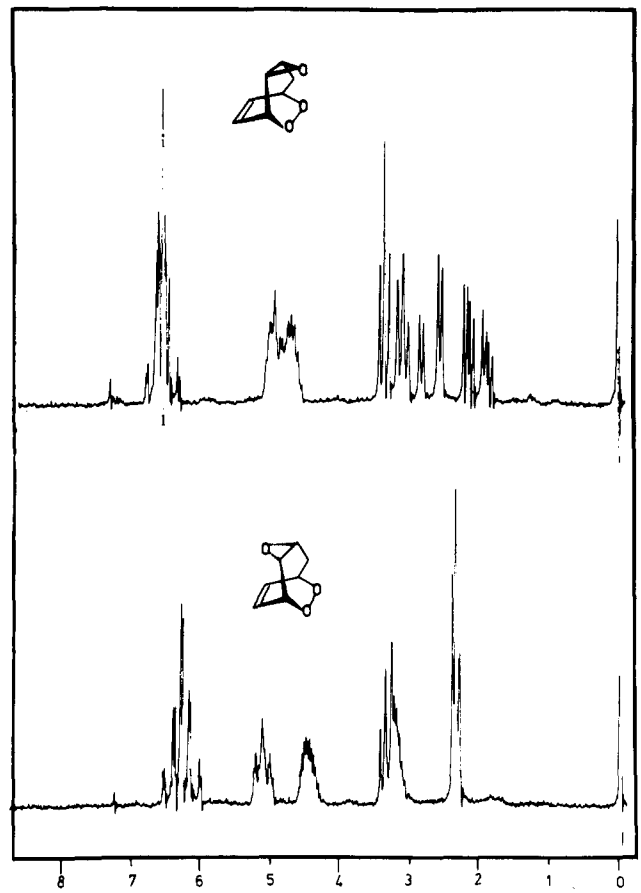
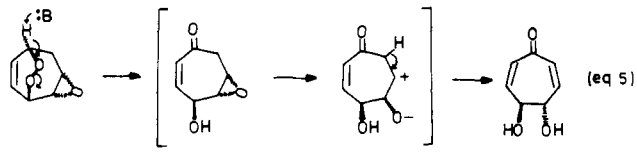


Figure 1. ^{1}H NMR spectra (60 MHz, Me_4Si) of *syn*-**2b** and *anti*-**2b** in $CDCl_3$.

combustion analysis for the $C_7H_8O_3$ elemental composition). The IR ($CHCl_3$) exhibited the characteristic hydroxyl OH at 3620–3200 cm^{-1}, the olefinic C—H at 3030 cm^{-1}, the conjugated enone C=O at 1665 cm^{-1}, and the conjugated C=C at 1610 cm^{-1}. The ^{1}H NMR ($CDCl_3$) using the double resonance technique was especially helpful in assigning the structure and stereochemistry of this interesting product. For example, the B part (trans H_5) of the AB pattern for the methylenic protons displayed a double doublet, which remained unchanged on irradiation of the epoxide protons $H_{6,7}$. In Dreiding models the $H_{5(trans)}$–H_6 dihedral angle is ~90°, thereby accounting for the small $J_{5(trans)6} < 0.5$ Hz coupling. The double of doublets thus arises from a large geminal coupling $J_{5(trans)5(cis)} = 13.82$ Hz and the large $J_{45(trans)} = 10.32$ Hz coupling. The latter coupling suggests that the H_4 and $H_{5(trans)}$ must have a trans geometry, which confirms that the 4-hydroxy substituent must be trans to the epoxide ring. Moreover, the appreciable $J_{27} = 1.83$ and $J_{24} = 2.66$ Hz long-range coupling must arise from the favorable W arrangements of these pairs of protons, as substantiated by inspection of Dreiding models. Furthermore, the triethylamine isomerization mechanism of *trans*-**2b** demands a trans configuration of the 4-hydroxy and 6,7-oxide substituents in hydroxy enone **5b**. Therefore, the hydroxy enone isomer **5a** obtained from *syn*-**2b** via triethylamine isomerization must be *cis*-**5a** (Scheme II).

As second eluate, eluting with 9:1 $CHCl_3$/MeOH the *trans*-**6b** diol was isolated, colorless oil (correct combustion analysis for the $C_7H_8O_3$ elemental composition). The IR and ^{1}H NMR data (cf. Experimental Section) substantiate the structure assignment. The mechanistic rationalization of the *trans*-**6b** diol is shown in eq 5. Presumably the β,γ-epoxy ketone is an intermediate, which is expected to isomerize readily to a 4-hydroxy 2-enone such as *trans*-**6b**. In that respect it is



anti-2b trans-5b

interesting to note that the isomeric α,β-epoxy ketone *trans*-**5b** that is formed in the triethylamine rearrangement of epoxy endoperoxide *anti*-**2b** survives the reaction conditions.

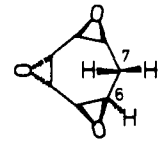
With the structure of the *anti*-**2b** epoxy endoperoxide assigned, let us now turn to its thermolysis as a synthetic route (Scheme I) to the syn,anti trioxide **3b** (Scheme III). Again high temperatures were necessary and at 190 °C for 1 h in toluene epoxy endoperoxide *anti*-**2b** rearranged into the desired *syn,anti*-**3b** trioxide in 44% yield, mp 66–67 °C, colorless plates (correct combustion analysis for the $C_7H_8O_3$ elemental composition), isolated and purified by silica gel chromatography and recrystallization from 1:2 CH_2Cl_2/Et_2O. The spectral data in Table I support the structure assignment. The ^{13}C NMR was particularly decisive for this purpose since this unsymmetrical trioxide exhibited six distinct epoxide-carbon and one methylene-carbon resonances. Again the off-resonance spectrum showed the expected doublets for the six epoxide carbons and a triplet for the methylene carbon.

Significant was the observation that the crude thermolysate mixture exhibited the presence of the diepoxide **7b** by IR and ^1H NMR. However, on silica gel chromatography, eluting with $CHCl_3$, as second eluate the trans hydroxy enone **5b** was isolated in 52% yield (Scheme III), which was identical with the sample prepared in the triethylamine isomerization of epoxy endoperoxide *anti*-**2b**. Since control experiments confirmed that the syn,anti trioxide **3b** was stable toward the thermolysis and silica gel conditions employed in the *anti*-**2b** → *syn,anti*-**3b** transformation, the precursor to the trans hydroxy enone **5b** must be the anti diepoxide **7b**. Presumably the silica gel catalyzes very readily the *anti*-**7b** → *trans*-**5b** isomerization since the diepoxide *anti*-**7b** possesses a β,γ-epoxy ketone moiety.[14] It is interesting, however, that the anti diepoxide **7b** formed in the thermolysis of anti epoxy endoperoxide **2b** is sufficiently stable to accumulate, while its syn isomer **7a** (eq 4) rearranged into the hydroxy enone *cis*-**5b**. The mechanistic history of *anti*-**7b** is rationalized analogously to that given in eq 4 for the *syn*-**2b** → *syn*-**7a** → *cis*-**5a** transformations.

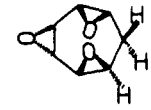
Anti,Anti Trioxide 3c. The stereospecific synthesis (Scheme I) of the third possible isomer, namely, the *anti,anti*-**3c** trioxide, engaged the [2 + 6] endoperoxide **1c**, which was obtained in 38% yield in the singlet oxygenation of cycloheptatriene.[7a] Thermolysis, but even better photolysis in benzene at 350 nm,[9] gave the syn diepoxide **2c** in 57% yield, which served as precursor to the desired anti,anti trioxide **3c**.

Examination of Dreiding models of the novel syn diepoxide **2c** product derived from the unusual endoperoxide–diepoxide rearrangement of **1c** suggested that peracid attack from the syn face should be blocked by the endo methylenic hydrogen. Indeed the syn diepoxide **2c** reacted slowly with excess *m*-chloroperbenzoic acid in CH_2Cl_2 over a period of 3 days to afford exclusively the anti,anti trioxide **3c** in 31% yield, mp 110–112 °C, colorless needles (correct elemental composition by high-resolution MS for the $C_7H_8O_3$ empirical formula), purified by recrystallization from 1:2 CH_2Cl_2/n-C_5H_{12}. The low yield of the trioxide is due to extensive deterioration of the syn diepoxide **2c** during the epoxidation. In fact, it was essential to run the *m*-chloroperbenzoic acid epoxidation in the presence of excess solid $NaHCO_3$ as proton range.

The structure assignment rests on the spectral data summarized in Table I. The ^{13}C NMR reveals a symmetric molecule, possessing the expected three distinct epoxide carbon and one methylene carbon resonances. The off-resonance spectrum confirms doublets for the epoxide carbons and a triplet for the methylenic carbon. By ^1H NMR it was possible to assign the diequatorial isomer as the preferred isomer in view



diequatorial-3c



diaxial-3c

of the large $J_{7(endo)6} = 8.19$ Hz coupling. For the diaxial conformer this coupling constant should be essentially zero because the $H_{7(endo)}$–H_6 dihedral angle appears to be ca. 90°. Of course, an X-ray analysis is in progress to substantiate this interesting stereochemistry of the anti,anti trioxide **3c**.

Conclusion

Returning to Scheme I, with relatively little synthetic effort we achieved the stereospecific preparation of the three possible cycloheptatriene trioxides, namely, the *syn,syn*-**3a**, *syn,anti*-**3b**, and *anti,anti*-**3c** isomers, all starting from the readily available 1,3,5-cycloheptatriene. A key transformation in their synthesis was the thermal and/or photolytic endoperoxide–diepoxide rearrangement (eq 1), which allows syn fixation of two adjacent epoxide rings. Equally valuable in the synthetic sequence was the difunctionalization of oxygen atoms through the convenient photosensitized oxygenation. The third oxygen functionality was introduced through the classical peracid epoxidation reaction. Therefore, the basic synthetic tools employed in this design were the singlet oxygenation (i), the endoperoxide rearrangement (ii), and the epoxidation (iii) reactions. However, by appropriate timing of these transformations in the synthetic sequence, the three trioxide isomers could all be prepared stereospecifically. In fact, the syn,syn trioxide **3a** was made from the same endoperoxide along two distinct pathways by permuting the endoperoxide rearrangement (ii) and epoxidation (iii) reactions, i.e., via the sequence (i), (ii), and (iii) vs. (i), (iii), and (ii). This valuable synthetic concept should prove useful in the design of complex oxygen functionalized target molecules derived from cyclic conjugated polyenes.

Experimental Section

Boiling points and melting points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 283 spectrophotometer, ^1H NMR spectra on a Hitachi Perkin-Elmer R-24B spectrometer, and mass spectra on a Hitachi Perkin-Elmer RMS-4 spectrometer. The elemental analyses were performed by the Atlantic Analytical Laboratories, P.O. Box 80569, Atlanta, Ga. 30366. Commercial reagents and solvents were purified to match reported physical and spectral data. Known compounds used in this research were either purchased from standard suppliers (if available) or prepared according to the literature procedures and purified to match the reported physical and spectral data.

Syn,Syn Trioxide 3a via Epoxidation of Ene Dioxide 2a (Route 1a → 2a → 3a). A solution of 0.27 mmol of **2a**, prepared by thermal endoperoxide rearrangement of **1a** as described previously,[11] and 0.7 mmol of *m*-chloroperbenzoic acid in 10 mL of CH_2Cl_2 was stirred for 48 h at 30 °C in the presence of solid $NaHCO_3$. The *m*-chlorobenzoic acid was extracted with aqueous 5% NaOH (2 × 10 mL), the organic layer dried over $MgSO_4$, the solvent rotoevaporated (20 °C at 10 Torr), and the residue chromatographed on silica gel at 25 °C, eluting with a mixture (2:1) of CH_2Cl_2/n-pentane. Recrystallization from 5:1 *n*-pentane/CH_2Cl_2 gave the pure substance, mp 159–162 °C (lit.[10] 165 °C), in 42% yield. The spectral data are summarized in Table I.

Syn,Syn Trioxide 3a via Thermolysis of Epoxy Endoperoxide *syn*-2b (Route 1a → *syn*-2b → 3a). A solution of 0.43 mmol of *syn*-**2b**, prepared by the epoxidation of endoperoxide **1a** as described below, in 3 mL of toluene was heated in a sealed tube for 1 h at 190 °C. Ro-

toevaporation of the solvent (25 °C at 10 Torr) and chromatography on silica gel at 25 °C eluting with CH_2Cl_2 gave as first fraction the syn,syn trioxide **3a** in 39% yield, mp 159–162 °C (lit.[2] mp 165 °C), after recrystallization from 1:5 CH_2Cl_2/*n*-pentane as colorless plates. The spectral data are summarized in Table I.

As second fraction, the trans hydroxy enone **5a** eluted with CH_2Cl_2 in 10% yield, mp 50–52 °C, recrystallized from ether as colorless prisms, which was identical with a sample prepared by triethylamine rearrangement of the epoxy endoperoxide *syn*-**2b** (experimental details described below).

Syn,Anti Trioxide 3b via Thermolysis of Epoxy Endoperoxide *anti*-2b (Route 1b → *anti*-2b → 3b). A solution of 1.64 mmol of *anti*-**2b,** prepared by singlet oxygenation of epoxide **1b** as described below, in 5 mL of toluene was heated in a sealed tube for 1 h at 190 °C. Rotoevaporation of the solvent (20 °C at 15 Torr) and chromatography on silica gel (20 g) at 25 °C eluting with a mixture (1:1) of $CHCl_3$/*n*-C_5H_{12} gave as first fraction the syn,anti trioxide **3b** in 44% yield, mp 66–67 °C, recrystallized from 1:2 CH_2Cl_2/Et_2O as colorless plates, correct combustion analysis for the $C_7H_8O_3$ elemental composition. The spectral data are summarized in Table I.

As second fraction, eluting with $CHCl_3$, the cis hydroxy enone **5b** was obtained in 52% yield, mp 35–38 °C, recrystallized from 3:2 ether/*n*-pentane as colorless needles, which was identical with a sample prepared by triethylamine rearrangement of the epoxy endoperoxide *anti*-**2b** (experimental details described below).

Anti,Anti Trioxide 3c via Epoxidation of Diepoxide 2c (Route 1c → 2c → 3c). A solution of 0.32 mmol of dioxide **2c,** prepared by photolytic endoperoxide rearrangement of **1c** as described previously,[11] and 0.96 mmol of *m*-chloroperbenzoic acid in 5 mL of CH_2Cl_2 was stirred for 72 h at 25 °C in the presence of solid $NaHCO_3$. The *m*-chlorobenzoic acid was extracted with aqueous 5% NaOH (2 × 10 mL), the organic layer dried over $MgSO_4$, the solvent rotoevaporated (25 °C at 10 Torr), and the residue chromatographed on silica gel at 25 °C, eluting with CH_2Cl_2. Recrystallization from 1:2 CH_2Cl_2/*n*-C_5H_{12} gave the analytically pure substance, mp 110–112 °C, as colorless needles in 31% yield, correct elemental composition for $C_7H_8O_3$ by high-resolution mass spectrometry. The spectral data are summarized in Table I.

Epoxy Endoperoxide *anti*-2b via Singlet Oxygenation of Cycloheptatriene Oxide (1b). A 50-mL, one-necked, pear-shaped flask was charged with a solution of 8.0 mmol of cycloheptatriene oxide (**1b**), prepared by peracetic acid epoxidation of cycloheptatriene,[15] and 1.0 mg of tetraphenylporphyrin (TPP) in 20 mL of CCl_4, and capped with a rubber septum. By means of an 18G stainless steel needle oxygen gas was allowed to bubble slowly through the reaction mixture, while venting with a 24G stainless steel needle, and the mixture was irradiated with a 400-W General Electric sodium street lamp at 0 °C, cooling by means of an ice bath. The progress of the singlet oxygenation was monitored by ^1H NMR, indicating that usually within 3 h the oxide **1b** had been consumed. The solvent was rotoevaporated (ca. 25 °C at 20 Torr) and the residue chromatographed on silica gel (15 g) at room temperature (ca. 30 °C) eluting with CH_2Cl_2. The product *anti*-**2b** was obtained in 68% yield, mp 125–127 °C after recrystallization from 1:4 CH_2Cl_2/Et_2O, as colorless plates, correct combustion analysis for the $C_7H_8O_3$ elemental composition. Spectral data: ^1H NMR ($CDCl_3$, Me_4Si) δ (ppm) 2.2–2.4 (2 H, m, H_7), 3.0–3.4 (2 H, m, $H_{1,2}$), 4.2–4.5 (1 H, m, H_6), 4.8–5.2 (1 H, m, H_3), and 5.8–6.4 (2 H, m, $H_{4,5}$); IR ($CHCl_3$) ν (cm^{-1}) 3020, 2980, 1520, 1230, 995, and 870; MS (70 eV) *m/e* 140.

Epoxy Endoperoxides *syn*-2b and *anti*-2b via Epoxidation of Endoperoxide 1a. A solution of 2.8 mmol of endoperoxide **1a,** prepared by singlet oxygenation of cycloheptatriene,[7] and 10 mmol of *m*-chloroperbenzoic acid in 40 mL of CH_2Cl_2 was refluxed for 36 h. The precipitate (*m*-chlorobenzoic acid) was removed by filtration, the filtrate extracted with aqueous $NaHSO_3$ (2 × 20 mL) and with aqueous $NaHCO_3$ (2 × 20 mL), and the organic layer dried over anhydrous $MgSO_4$. Rotoevaporation of the solvent (ca. 25 °C at 10 Torr) and silica gel (15 g) chromatography at room temperature (ca. 30 °C) eluting with 2:1 CH_2Cl_2/*n*-C_5H_{12} gave as first eluate *anti*-**2b** in 11% yield, identical in its physical and spectral properties as described above for the singlet oxygenation of endoperoxide **1a.**

As second eluate the *syn*-**2b** epoxy endoperoxide was isolated in 35% yield, mp 101–103 °C, recrystallized from ether as colorless plates, correct combustion analysis for the $C_7H_8O_3$ elemental composition. Spectral data: ^1H NMR ($CDCl_3$, Me_4Si) δ (ppm) 2.06 (1 H, ddd, endo methylenic H_7), 2.7 (1 H, dd, exo methylenic H_7), 3.1 (1 H, t, H_1), 3.35 (1 H, t, H_2), 4.5–4.8 (1 H, m, H_6), 4.8–5.1 (1 H, m, H_3), 6.3–6.8 (2 H, m, $H_{4,5}$) with J_{12} = 4.0, J_{23} = 4.3, $J_{67(exo)}$ = 3.6, $J_{17(endo)}$ = 5.5, $J_{67(endo)}$ = 3.4, J_{77} = 16.7, $J_{17(exo)} \sim 0$ Hz; IR (KBr) ν (cm^{-1}) 3000, 2905, 1455, 1430, 1395, 1265, 1160, 1045, 1005, 990, and 965.

***anti*-6,7-Dioxabicyclo[3.2.2]nonane 2,3-Oxide (4b) via Diimide Reduction of *anti*-2b Epoxy Endoperoxide.** A 50-mL, three-necked, round-bottom flask, provided with magnetic spin bar, 20-mL pressure-equalizing addition funnel, and nitrogen inlet and outlet tubes, was charged with 5 mmol of potassium azodicarboxylate in 10 mL of dry CH_2Cl_2. The slurry was cooled to 0 °C and a solution of 0.32 mmol of epoxy endoperoxide *anti*-**2b** in 2 mL of CH_2Cl_2 was added. While cooling and stirring a solution of 10 mmol of HOAc in 5 mL of CH_2Cl_2 was added dropwise within ca. 20 min and stirred until complete discharge of the characteristic yellow azodicarboxylate color. Subsequently 20 mL of H_2O was added slowly, and the organic layer was extracted with saturated, aqueous $NaHCO_3$ (2 × 10 mL) and washed with water. After drying over $MgSO_4$, the solvent was rotoevaporated (ca. 25 °C at 10 Torr) and the waxy residue sublimed (60 °C and 0.5 Torr), affording a 90% yield of *anti*-**4b,** mp 134–137 °C, as a colorless wax, correct combustion analysis for the $C_7H_{10}O_3$ elemental composition. Spectral data: ^1H NMR ($CDCl_3$, Me_4Si) δ (ppm) 1.4–2.2 (4 H, m, methylene), 2.2–2.5 (2 H, m, methylene), 3.1–3.5 (2 H, m, epoxide), 4.0–4.4 (1 H, m, bridgehead), and 4.45–4.8 (1 H, m, bridgehead); IR ($CDCl_3$) ν (cm^{-1}) 3020, 3000, 2960, 1460, 1105, 990, 930, 800.

***syn*-6,7-Dioxabicyclo[3.2.2]nonane 2,3-Oxide (4b) via Diimide Reduction of *syn*-2b Epoxy Endoperoxide.** The same procedure as described above for the *anti*-**4b** isomer was employed. The *syn*-**4b** was obtained in 72% yield, mp 113 °C (sublimed at 60 °C and 1 Torr), as a colorless wax, correct combustion analysis for the $C_7H_{10}O_3$ elemental compositon. Spectral data: ^1H NMR ($CDCl_3$, Me_4Si) δ (ppm) 1.5–2.5 (6 H, m, methylene), 2.8–3.1 (2 H, m, epoxide), and 4.0–4.7 (2 H, m, bridgehead); IR ($CHCl_3$) ν (cm^{-1}) 3040, 2980, 1415, and 1200.

***cis*-4-Hydroxycyclohept-2-enone 6,7-Oxide (5a) via Triethylamine Isomerization of Epoxy Enone *syn*-2b.** A solution of 0.42 mmol of *syn*-**2b** and 0.84 mmol of Et_3N in 15 mL of CH_2Cl_2 was stirred at room temperature (ca. 30 °C) for 4 h. Rotoevaporation of the solvent (25 °C at 10 Torr) and silica gel (5 g) chromatography at room temperature eluting with CH_2Cl_2 gave the hydroxy enone *cis*-**5a** in 63% yield, mp 50–52 °C, recrystallized from Et_2O as colorless prisms, correct combustion analysis for the $C_7H_8O_3$ elemental composition. Spectral data: ^1H NMR ($CDCl_3$, Me_4Si) δ (ppm) 2.0–3.1 (2 H, AB system, H_5), 3.5–3.7 (2 H, m, $H_{6,7}$), and 4.0–4.6 (1 H, m, H_4), and 5.8–6.9 (2 H, AB system, $H_{2,3}$) with J_{23} = 13.2, J_{34} = 7.00, J_{27} = 1.8, $J_{35(cis)}$ = 1.1, $J_{5(cis)5(trans)}$ = 14.5, and $J_{45(cis)}$ = 2.7 Hz; IR ($CHCl_3$) ν (cm^{-1}) 3600, 3050, 2970, 1630, and 1415.

***trans*-4-Hydroxycyclohept-2-enone 6,7-Oxide (5b) and *trans*-4,5-Dihydroxycyclohepta-2,6-dienone (6b) via Triethylamine Isomerization of Epoxy Enone *anti*-2b.** The same procedure as described above for the *syn*-**2b** isomer was employed, except that the isomerization was conducted at 0 °C. Silica gel (10 g) chromatography at room temperature (ca. 30 °C) eluting with $CHCl_3$ gave as first eluate the *trans*-**5b** product in 65% yield, mp 35–38 °C, recrystallized from 3:2 ether/*n*-pentane as colorless needles, correct combustion analysis for the $C_7H_8O_3$ elemental composition. Spectral data: ^1H NMR ($CDCl_3$, Me_4Si) δ (ppm) 1.85–2.85 (2 H, m, H_5), 3.1 (1 H, m, OH), 3.2–3.6 (2 H, m, $H_{6,7}$), 4.2–4.6 (1 H, m, H_4), and 5.45–6.5 (2 H, AB system, $H_{2,3}$) with J_{23} = 12.3, J_{24} = 2.66, J_{27} = 1.83, J_{34} = 1.66, $J_{35(cis)}$ = 1.66, $J_{5(cis)5(trans)}$ = 13.82, $J_{45(trans)}$ = 10.32, $J_{45(cis)}$ = 3.66, and $J_{5(trans)6} \sim 0$ Hz; IR ($CHCl_3$) ν (cm^{-1}) 3620, 3200, 3030, 1665, 1610, 1230, 1040, and 800.

On elution with 20:1 $CHCl_3$/MeOH a second eluate was obtained in 27% yield as a colorless liquid, correct combustion analysis for the $C_7H_8O_3$ elemental composition. The trans diol **6b** structure was identified on the basis of the following spectral data: ^1H NMR (acetone-d_6, Me_4Si) δ (ppm) 4.25 (2 H, br s, $H_{4,5}$), 4.4–4.5 (2 H, m, OH), and 5.5–6.45 (4 H, AB system, $J_{2,3}$ = $J_{6,7}$ = 11.6 Hz, $H_{2,3,6,7}$); IR (neat) ν (cm^{-1}) 3700–3100, 1665, and 1615.

Control Experiments. Thermal Stability of Syn,Syn Trioxide 3a. On heating a solution of 0.1 mmol of **3a** in 1 mL of toluene in a sealed tube for 1 h at 190 °C (thermolysis conditions of *syn*-**2b** → **3a**) the sample was recovered unchanged as confirmed by ^1H NMR.

Silica Gel Stability of Syn,Syn Trioxide 3a. Stirring a solution of 0.1 mmol of **3a** in 10 mL of $CHCl_3$ in the presence of silica gel for 2

h at room temperature (chromatography conditions of trioxide **3a**) led to recovery of the trioxide **3a** as confirmed by ^{1}H NMR.

Thermal Stability of Syn,Anti Trioxide 3b. Heating a solution of 0.1 mmol of **3b** in 1 mL of toluene in a sealed tube for 1 h at 190 °C (thermolysis conditions of *anti*-**2b** → **3b**) gave unchanged **3b** as confirmed by ^{1}H NMR.

Silica Gel Stability of Syn,Anti Trioxide 3b. Stirring a solution of 0.1 mmol of **3b** in 10 mL of CH_2Cl_2 in the presence of silica gel for 3 h at room temperature (chromatography conditions of trioxide **3b**) afforded **3b** unchanged as confirmed by ^{1}H NMR.

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Mercury in Organic Chemistry. 17. A Convenient Stereospecific Synthesis of Enol Esters from Vinylmercurials

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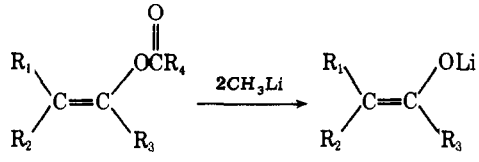
Abstract: The room temperature reaction of vinylmercurials, mercury carboxylates, and a catalytic amount of palladium acetate provides a novel stereospecific route to a variety of enol carboxylates. The mercuration and subsequent palladium-catalyzed esterification of internal acetylenes afford trans ene diacetates in a convenient one-pot procedure. Lead tetraacetate also reacts with vinylmercurials to afford enol acetates.

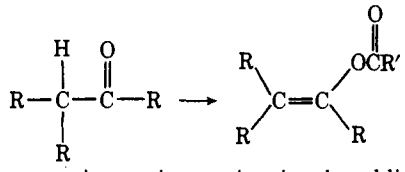
Enol esters have proven to be extremely valuable intermediates in organic synthesis. Epoxidation[2-11] or halogenation[12-20] of these compounds affords α-acyloxy- or α-halocarbonyl compounds. Photolysis,[21] reduction,[22] acylation, and rearrangement[23-36] all result in carbon–carbon bond formation. One especially important application of enol esters lies in their facile conversion to regio- and stereospecific lithium enolates upon treatment with methyllithium (eq 1).[37-43] Very



(1)

few general methods are available for the stereospecific generation of such enolates in spite of their widespread utility in organic synthesis.

Unfortunately, relatively few methods are presently available for the synthesis of enol esters. The most widely practiced technique involves the treatment of aldehydes or ketones under either acid or basic conditions with the appropriate acid anhydride or chloride (eq 2).[2,7,12,13,16,17,30,37-39,42-61] Other major



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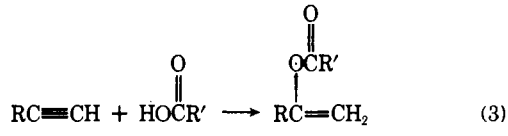
methods for preparing enol esters involve the addition of carboxylic acids to alkynes[62-81] (eq 3 and 4) and the palladium-promoted acetoxylation of olefins (eq 5 and 6).[82,83] Although limited in scope, vinyl acetate can be arylated using arenes,[84-86] triarylphosphines,[87] or arylmercurials[88-90] and palladium catalysts (eq 7).



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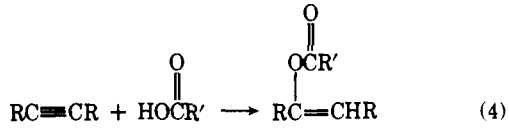

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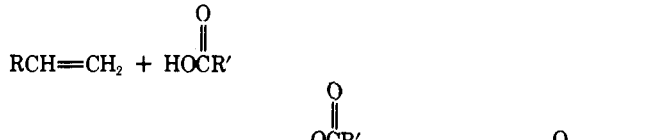

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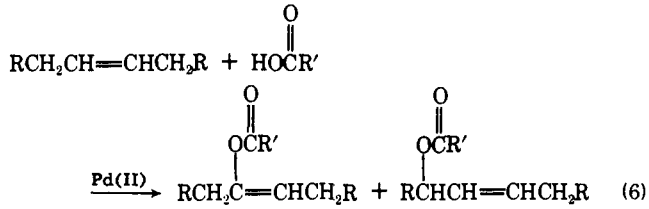

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