Preparative Visible-Laser Photochemistry: Qinghaosu-Type 1,2,4-Trioxanes by Molecular Oxygen Trapping of Paterno-Büchi Triplet 1,4-Diradicals Derived from 3,4-Dihydro-4,4-dimethyl-2*H*-pyran-2-one and Quinones

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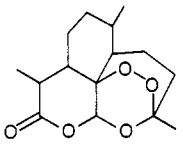
The visible-laser photochemistry of 3,4-dihydro-4,4-dimethyl-2*H*-pyran-2-one (1) with benzoquinone (BQ) and with phenanthraquinone (PQ) in an argon atmosphere afforded the expected regioisomeric oxetane products **2** and **3**. Under an oxygen atmosphere, trapping of the Paterno–Büchi preoxetane intermediates by molecular oxygen was observed for BQ, leading to the regioisomeric and stereoisomeric 1,2,4-trioxanes **4**-BQ and **5**-BQ. Regioselectivity, favoring the acetal-type structures **2** and **4**, appears to follow diradical stability. Anomeric effects are invoked to rationalize the stereochemical course of the trioxane trapping products. The lactone–acetal structure **4** represents the first qinghaosu-type (artemisinin) 1,2,4-trioxane.

The antimalarial drug artemisinin, in Chinese folk medicine long known as qinghaosu, has received in recent years much attention in view of its high pharmacological activity but low toxicity.[1] The unique structural feature



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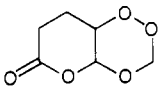
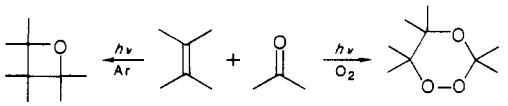


1,2,4-trioxane lactone

is the 1,2,4-trioxane lactone structure, which is essential for its biological action.[2] Isolation of larger quantities of this so far only natural 1,2,4-trioxane structure from plant material has been cumbersome, so that two total syntheses[3] have been performed to provide a more convenient chemical source. Nevertheless, the need to devise more efficient synthetic methodology for this challenging structure persists, which stimulated the present model studies.

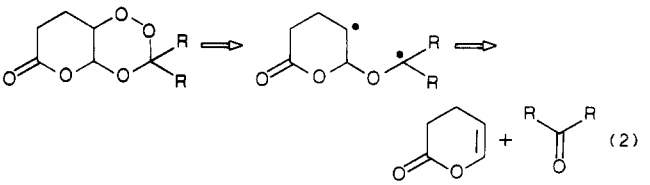
Of the available methods for the preparation of the 1,2,4-trioxane ring system must be mentioned acid-catalyzed cyclization of β-hydroperoxy alcohols with ketones[4] and of α-hydroperoxy alcohols with epoxides,[5] the autoxidation of imines in the presence of aldehydes,[6] the acid-catalyzed incorporation of aldehydes into endoperoxides and dioxetanes,[7] and the trapping of Paterno–Büchi triplet 1,4-diradicals by molecular oxygen.[8] In the latter synthetic concept, which shall be utilized in the present model study, n,π^* excitation of the carbonyl component in the presence of an olefin partner under an oxygen atmosphere leads to the desired 1,2,4-trioxane (eq 1). Since



(1)

molecular oxygen is an efficient quencher of carbonyl excited states, since Paterno–Büchi triplet 1,4-diradicals are short-lived (τ < 5 ns) species[9] and thus inefficiently trapped under bimolecular conditions, and since peroxides are generally photolabile, the use of an argon ion laser is particularly advantageous, because it supplies a high intensity of monochromatic radiation continuously.

We report here the synthesis of the 1,2,4-trioxane lactone structural unit that is contained in the qinghaosu molecule, following the retrocyclic sequence outlined in eq 2. 3,4-



(2)

Dihydro-4,4-dimethyl-2*H*-pyran-2-one (1)[10] was chosen as enol lactone component, and *p*-benzoquinone (BQ) and phenanthraquinone (PQ) were chosen as carbonyl components. The *gem*-dimethyl substitution in the enol lactone **1** was desirable to suppress possible ene reactions with singlet oxygen, a prominent species in the quenching of n,π^* carbonyl triplet states by molecular oxygen during laser irradiation. The choice of BQ and PQ as carbonyl components was dictated by the fact that these quinones absorb in the visible region, where the argon ion laser possesses intense lines, the triplet character of their n,π^* excited states is well defined,[11] and the peroxide products (1,2,4-trioxanes) are expected to be quite photostable toward visible light.

Results

Product Studies. The expected photoproducts of the Paterno–Büchi reaction of 3,4-dihydro-4,4-dimethyl-2*H*-pyran-2-one (1) with benzoquinone (BQ) and phenan-

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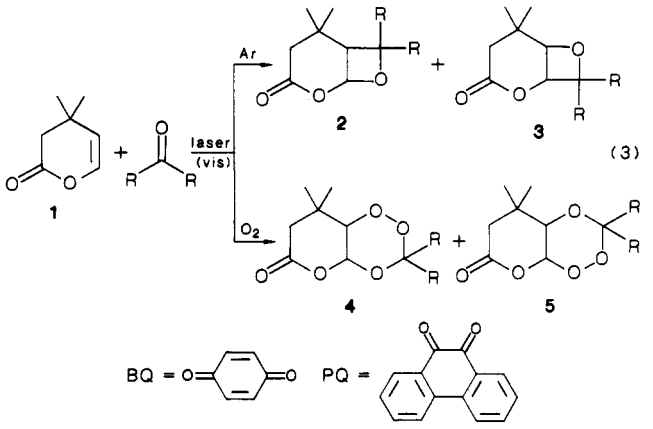
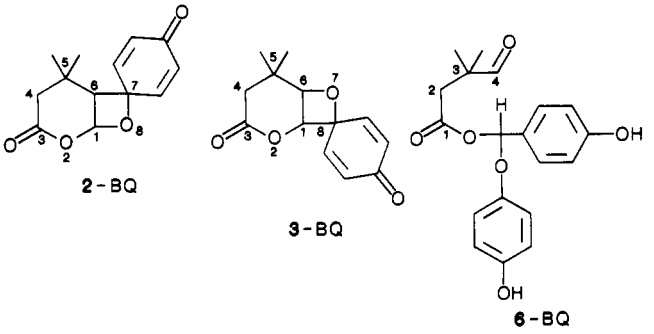
thraquinone (PQ) in argon or oxygen atmosphere are given in the general scheme of eq 3, in which only the possible



(3)

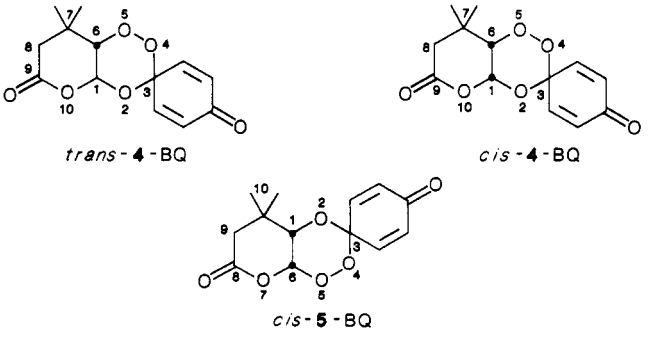
regioisomers but not stereoisomers are specified. The acronyms BQ and PQ will be used with the structure numerals **2–5** to recognize readily the carbonyl partner in the photoproducts.

In the photocycloaddition of **1** with BQ under argon atmosphere, after ca. 5 h of irradiation at 455–515 nm (Coherent supergraphite argon ion laser CR18) in dry CCl_4, 95% conversion was achieved, leading to the oxetane **2-BQ** and the double adduct **6-BQ** in a product balance of 42% and 95:5 relative proportion (by ^1H NMR). By means of



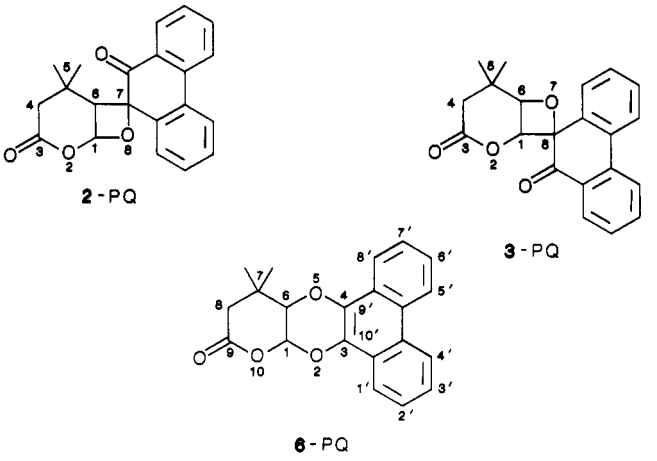
chromatography it was not possible to isolate from the complex product mixture further definitive photoproducts. In the ^1H NMR spectrum of the crude photolysate, the regioisomeric oxetane **3-BQ** could not be detected.

In an oxygen atmosphere, visible-laser irradiation for ca. 6 h led to complete consumption of the starting materials, affording, in addition to the regioisomeric oxetanes **2-BQ** and **3-BQ**, the 1,2,4-trioxanes *trans*-**4-BQ**, *cis*-**4-BQ**, and *cis*-**5-BQ**. The product balance of the BQ photoproducts



2, **3**, *trans*-**4**, *cis*-**4**, and *cis*-**5** was ca. 65%, in relative yields (by ^1H NMR, normalized to 100%) of 28:17:28:9:18, respectively. Thus, the proportion of oxetane to 1,2,4-trioxane products was 45:55. The oxetane regioisomer **3-BQ**, which was not detected in the irradiations under argon, could not be isolated in pure form even by preparative HPLC in view of its labile nature. The pyranone **1** was inert toward photooxygenation, using tetraphenylporphyrin as sensitizer. The 1,2,4-trioxanes **4-BQ** and **5-BQ** were stable under the photolysis conditions.

The photocycloaddition of phenanthraquinone (PQ) with pyranone **1** under argon atmosphere gave after 2.3 h (ca. 90% conversion) the oxetanes **2-PQ** and **3-PQ** and the Schönberg-type adduct **6-PQ** in a product balance of



95% and relative yields (by ^1H NMR, normalized to 100%) of 64:26:10, respectively. The oxetane **3-PQ** was photolabile and on prolonged irradiation afforded the Schönberg product **6-PQ**.

Rather similar results were obtained with PQ and **1** under an oxygen atmosphere. In a product balance of 84%, the relative yields of **2-PQ**, **3-PQ**, and **6-PQ** were 51:32:17, respectively. No corresponding 1,2,4-trioxanes could be detected in the crude photolysate by ^1H NMR (400 MHz).

Structure Assignments. Oxetanes 2 and 3. The IR spectra show the lactone carbonyl absorption in the expected range 1750–1760 cm^{-1} for all the oxetanes that were isolated. Oxetane **2-BQ** in addition exhibits the dienone carbonyl group in the form of two intensive stretchings at 1630 and 1670 cm^{-1}, while the conjugated carbonyl absorptions in **2-PQ** and **3-PQ** are visible at 1700 cm^{-1}.

The ^1H and ^{13}C NMR spectra were definitive in assigning the structures. The methylenic protons of the lactone ring (position 4) exhibit an AB pattern with J_{AB} ~17–18 Hz. The B part of these signals is further split by the bridgehead proton 6-H, which enabled an unequivocal differentiation of the oxetane protons 1-H and 6-H.

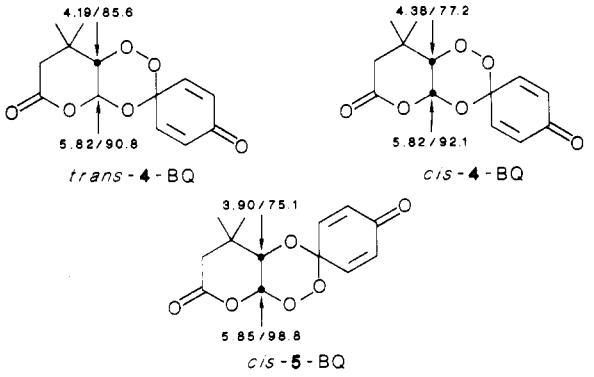
Comparison of the NMR shifts of **3-PQ** with those of **3-BQ**, which could not be isolated in pure form, allowed rigorous assignment from the spectra of the crude photolysate. For the 1-H protons, the resonances are δ 5.18 and 5.12 for **3-BQ** and **3-PQ**, and for the 6-H protons, δ 4.81 and 4.91, respectively. In contrast, for the **2-BQ** and **2-PQ** regioisomers, the 1-H protons have δ 6.25 and 6.41 and the 6-H protons δ 3.12 and 2.99. Equally clear-cut are the carbon resonances in that for **3-BQ** and **3-PQ** the C-1 carbon atoms are positioned at δ 80.6 and 79.5, respectively, and the C-6 carbon atoms at δ 79.2 and 78.5. However, for the **2-BQ** and **2-PQ** regioisomers, the C-1 carbon atoms come at δ 99.0 and 98.3 and the C-6 at δ 54.1 and 50.5. These trends in ^1H and ^{13}C chemical shifts substantiate the acetal functionality in the oxetane regioisomers **2** and the *vic*-dialkoxy one in the **3** series.

More cumbersome was the stereochemical assignment of the phenanthrene moiety in the photoadducts **2-PQ** and **3-PQ**. On the basis of ^1H NMR data, it was difficult to

make a rigorous choice whether the carbonyl group of the phenanthrene moiety was syn or anti to the lactone ring. Fortunately, an X-ray structure determination on **2**-PQ (Figure 1, Table I) unequivocally established the anti diastereomer. For the regioisomer **3**-PQ, the anti configuration is inferred.

1,2,4-Trioxanes 4 and 5. As expected, the IR spectra for the BQ photoproducts exhibit strong lactone carbonyl absorption at 1770 cm^{-1}. In addition, two carbonyl bands for the dienone group are observed at 1640 and 1690 cm^{-1}.

Quite analogously to the oxetanes **2** and **3**, the lactone CH_2 group was observed as an AB pattern with $J_{AB} \sim 18$ Hz. Differentiation of the bridgehead protons 1-H and 6-H and carbon atoms C-1 and C-6 rests on chemical-shift arguments. This assignment is more difficult for the regioisomeric 1,2,4-trioxanes **4** and **5** than for the regioisomeric oxetanes **2** and **3** because one must distinguish between the acetal–peroxide combination in **4** versus peroxyacetal–ether combination in **5**. The pertinent characteristic NMR data are specified in the structural formulas shown and provide for an internally consistent



assignment. The X-ray structure determination of the 1,2,4-trioxane *trans*-**4**-BQ (Figure 1, Table II) was most helpful in differentiating between these regioisomers. The stereochemistry of the C-1/C-6 ring junction in *trans*-**4**-BQ is also evident from its X-ray structure (Figure 1). That the other stereoisomer was *cis*-**4**-BQ could be assessed by temperature-dependent line broadening in the ^1H NMR spectrum. While *trans*-**4**-BQ exhibited sharp lines over the temperature range 200–300 K, for *cis*-**4**-BQ we observed broad absorptions at ca. 300 K. A similar phenomenon and a double set of proton resonances at ca. 220 K were noticed for *cis*-**5**-BQ. Ring inversion is only feasible for the cis conformer, because the trans conformer is perfectly rigid.

Photoproducts 6-BQ and 6-PQ. The minor product **6**-BQ, obtained in the *p*-benzoquinone photoaddition with the pyranone **1**, possesses the aldehyde function, as evidenced by its characteristic C–H absorption at 2740 cm^{-1} and C=O absorption at 1690 cm^{-1} in the IR spectrum, its carbon resonance at δ 191.4 as a doublet, and its proton resonance at δ 9.84 as a singlet. The latter fact requires *gem*-dimethyl substitution of the α-carbon (position 3). The O–H absorptions are clearly evident at 3200–3350 cm^{-1} in the IR spectrum and the phenol moieties by the characteristic chemical shifts and patterns of the aromatic protons and carbon atoms in its NMR spectra. The acetal functionality is recognized by its proton absorption at δ 5.15 as a singlet and by its carbon resonance at δ 89.9 as a doublet. The carbonyl band at 1770 cm^{-1} and the carbon resonance at δ 177.2 speak for the ester group. All these structural characteristics are best accommodated in the form of the **6**-BQ structure for this secondary photolysis product.

The structure of the Schönberg product **6**-PQ was adduced on the basis of spectral and analytical data. The carbonyl group shows absorption at 1750 cm^{-1} in the IR spectrum. The bridgehead protons 1-H and 6-H occur as singlets ($J_{1,6} \sim 0$ Hz) at δ 6.28 and 4.04, which suggests the cis configuration. For trans stereochemistry, a substantial coupling ($J_{1,6} > 10$ Hz) would have had to be expected.[12] The bridgehead carbon atoms C-1 and C-6 are located at δ 92.8 and 73.3 as doublets.

Discussion

The present results demonstrate that it is feasible to construct the simplest enol lactone trioxane skeleton contained in qinghaosu via oxygen trapping of the intermediary Paterno–Büchi triplet 1,4-diradical, as outlined in the retrosynthetic sequence of eq 2. To date, only one example, namely, the oxygen trapping of the preoxetane intermediate derived from vinyl acetate and BQ, has been reported,[8] leading to such a functionalized monocyclic 1,2,4-trioxane. Of the two carbonyl partners employed here, only BQ afforded the two possible regioisomeric trioxanes **4**-BQ and **5**-BQ, PQ giving exclusively the oxetane products **2**-PQ and **3**-PQ as well as the Schönberg product **6**-PQ. Although the normal photocycloaddition (argon atmosphere) works more efficiently for PQ than BQ, leading to cleaner product mixtures (product balances of ca. 95% versus 42% for PQ and BQ, respectively; corrected for extent of conversion), no evidence for oxygen trapping of the preoxetane species derived from PQ and enol lactone **1** could be provided, since not even traces of peroxidic products (trioxanes **4**-PQ and **5**-PQ) were observed in the crude photolysate. This is puzzling, if one realizes that for BQ and pyranone **1** the oxygen trapping products predominate, i.e., 55% relative yield of all BQ trioxanes versus 45% of all BQ oxetanes (65% product balance).

The divergent behavior between PQ and BQ in regard to oxygen trapping of preoxetane diradicals appears to be general. For example, in the Paterno–Büchi cycloaddition of 1,4-dihydrodioxin, trioxane products are formed with BQ[13] but not with PQ.[14] Furthermore, with the related α-dicarbonyl compound biacetyl also no oxygen trapping of the 1,4-diradical was observed.[9] As in the latter study, we can only speculate on the mechanistic reason for the lack of oxygen trapping of PQ-derived preoxetane species. Surely, the causes must relate to the electronic nature, i.e., zwitterionic versus diradical states, to the spin state, i.e., singlet versus triplet diradicals, and to the lifetime of such intermediates.[15] Recent studies[16] reveal that trapping by molecular oxygen is observed for triplet diradicals with lifetime $\tau > 1$ ns.

The structures of the zwitterions and triplet diradicals of the predominating BQ- and PQ-derived preoxetane regioisomers **7** and **8**, respectively, need to be scrutinized. Compared to the BQ-derived preoxetanes, for which the triplet diradical state **8**-BQ must dominate in view of efficient trapping by $^3O_2$ (i.e., 55% trioxane product), for the PQ-derived preoxetane either the zwitterionic form **7**-PQ prevails or the lifetime of its triplet diradical **8**-PQ is much shorter. To estimate the lifetime, it should be recalled that

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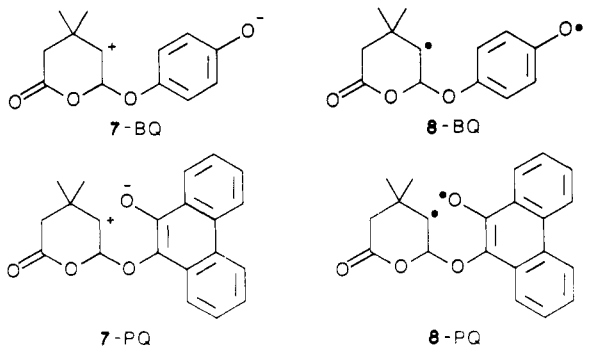
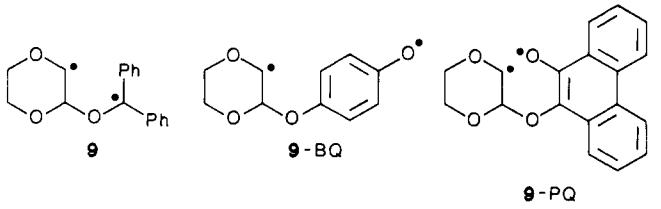
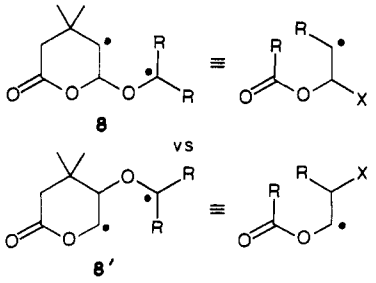


for the triplet 1,4-diradical 9 $\tau \sim 2$ ns, as determined by time resolved laser flash spectroscopy.[17] Thus, the lifetimes of the related BQ-derived species 8-BQ and 9-BQ



must be at least that high because oxygen trapping of these is more efficient than for 9.[13,14] In view of the fact that no trioxanes were observed for the preoxetanes 8-PQ and 9-PQ,[14] their triplet lifetimes must be significantly lower than 1 ns. Since the lifetime of triplet diradicals is dictated by the rate of intersystem crossing,[15,16] it is not immediately obvious why for these aryloxy-type structures spin slip should be so much faster (in view of the above estimated triplet lifetimes at least 10-fold) in 8-PQ than in 8-BQ to preclude oxygen trapping of the former. We postulate that for the more delocalized phenanthryloxy species zwitterionic contributions such as 7-PQ play a dominant role, mixing in singlet-state character more effectively and consequently facilitating intersystem crossing and thus shorter triplet lifetimes. Alternatively, the enol lactone–PQ exciplex generates directly under charge transfer or even electron transfer the zwitterion 7-PQ without traversing the triplet 1,4-diradical 8-PQ.[9] Recent work[18] on the Paterno–Büchi reaction of biacetyl with ketene acetals argues in favor of such happenstance. Clearly, time resolved laser flash photolysis work is in order to resolve this mechanistic incognito.

Of unquestionable interest are the observed regioselectivities, i.e., the preferred oxetane 2 and trioxane 4 regioisomers for both BQ and PQ, especially since for qinghaosu-type trioxanes the Paterno–Büchi triplet 1,4-diradical 8 (attack at 6-position) rather than 8′ (attack at

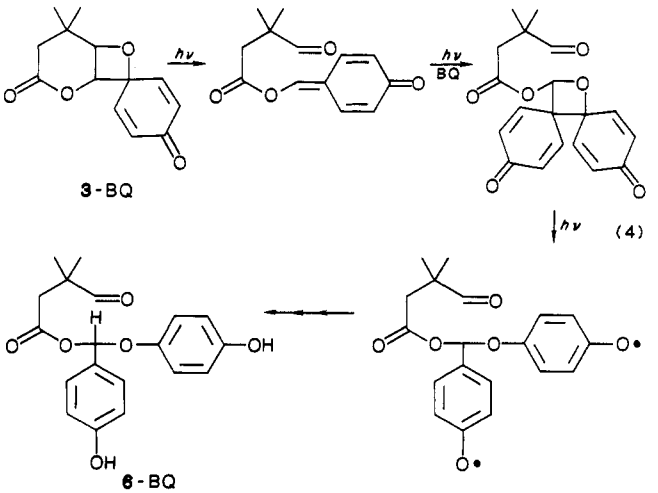


5-position) is required. On the basis of frontier orbital theory on the Paterno–Büchi reaction,[19] the criterion that attack should take place at the site of the largest HOMO coefficient in the enol ester (calculated by MNDO[20]) would

predict a slight preference for the regioisomer 8′. This is in contrast to our experimental finding, since regioisomer 8 predominates.

Radical stabilization energies (RSE) provide for better qualitative insight.[21] Approximating the pyranone 1 as an alkyl-substituted enol ester, the hypothetical radical structural unit resembling 8 is by ca. 1–2 kcal/mol more stable than that resembling 8′ because alkyl stabilization of a radical site dominates over acyloxy stabilization. Consequently, it is not surprising that the oxetanes 2 and trioxanes 4 prevail over the corresponding regioisomers 3 and 5.

At first sight it appears that in the Paterno–Büchi reaction of enol lactone with BQ exclusively the oxetane 2-BQ is formed. However, we postulate that the aldehyde 6-BQ is the secondary photoproduct derived from the regioisomer 3-BQ for the following reasons. In the photocycloaddition under oxygen gas pressure, the labile oxetane 3-BQ is obtained, although it was not possible to isolate it in pure form. Furthermore, the related oxetane 3-PQ is photolabile, and under the laser-irradiation conditions of the Paterno–Büchi reaction, it is isomerized to the Schönberg product 6-PQ. A reasonable mechanism for the 3-BQ → 6-BQ photoreaction is given in eq 4. What is



unusual is that in the laser irradiation under oxygen pressure some of the photolabile oxetane 3-BQ survives; apparently $^3O_2$ exercises photoprotection.

It remains to comment on the stereoselectivity in the formation of the trioxanes 4-BQ and 5-BQ. The latter is only observed as the cis isomer, while the former exists as a cis, trans mixture, the trans isomer predominating by ca. 3-fold. We propose that stereoelectronic factors such as the anomeric effect[22] in the intermediary Paterno–Büchi

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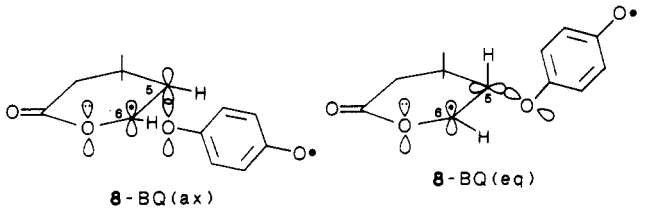
triplet 1,4-diradicals play a role. Without entering into the conformational details of the δ-lactone ring, i.e., chair, half-chair, boat, etc. (for that, either quantum chemical or molecular mechanical computations would have to be performed on these open shell systems), the preferred conformer resulting from attaching the phenoxy fragment at the C-5 position appears to be the axial one, i.e., 8-BQ(ax), since exclusively the 1,2,4-trioxane *cis*-**5**-BQ is



formed. As suggested for the 1-pyranosyl radicals,[22] the anomeric interaction between the 2p orbital at the radical site C-6 and the σ* orbital of the carbon–oxygen bond of the β-aryloxy substituent at C-5 is magnified by the conjugative interaction of the adjacent oxygen lone pair at O-1. Such a magnified anomeric effect is absent in the 8-BQ(eq) conformer.

In summary, novel lactone trioxanes of the qinghaosu type can be prepared by molecular oxygen trapping of the Paterno–Büchi triplet 1,4-diradicals derived from pyran-2-one **1** and *p*-benzoquinone. This potentially useful synthetic methodology has been extended to the exo-methylenic enol lactones $\Delta^{1,6}$-2-oxabicyclo[4.4.0]decen-2-one[23] and 4-penten-4-olide,[24] yielding spiro-annelated lactone trioxanes as novel qinghaosu analogues.

Experimental Section

For preparative HPLC separations, a LiChrospher Si 100 (5 μm) column (250 mm × 20 mm) was employed. For laser irradiations, a Coherent supergraphite argon ion laser (CR18) with UV optics (λ = 333.6, 351.4, 363.8 nm; ca. 2.8 W) and with visible optics (λ = 454.5, 457.9, 465.8, 472.7, 476.5, 488.0, 496.5, 501.7, 514.5 nm; 5–6 W) was used. The laser output was monitored with a Coherent Radiation Model 201 thermal disk power meter. The laser beam was always expanded by means of a lens, before being focused onto the reaction vessel. The photoreactions were run in a Griffin–Worden tube,[8] supplied with a magnetic spinbar and aluminum-encased water jacket for cooling and protection.

Commercial reagents and solvents were purchased from standard chemical suppliers and purified to match the reported physical and spectral data. Known compounds were prepared according to literature procedures and purified accordingly.

General Procedure for the Laser Irradiations. Equimolar amounts of the 3,4-dihydro-4,4-dimethyl-2*H*-pyran-2-one (**1**) and the carbonyl components *p*-benzoquinone (BQ) and *o*-phenanthraquinone (PQ) in ca. 30 mL of absolute CCl_4 (ca. 0.1 M) or $CFCl_3$ (ca. 0.05 M) respectively were placed into a Griffin–Worden tube and degassed by five freeze–pump–thaw cycles, the solution being saturated in the last cycle with either argon (ca. 1 atm) or oxygen (ca. 10 atm) gas. While being stirred vigorously, the reaction mixture was irradiated at ca. −5 °C with an expanded beam of laser light. The consumption of starting materials was monitored by TLC or ^{1}H NMR until there was no further color change of the often cloudy yellow-orange photolysate mixture. The solvent was removed by rotaevaporation (ca. 20 °C at 20 Torr) and the residue purified by flash chromatography on silica gel. In all cases, unidentified, higher molecular weight products were retained on the column, which was responsible for the low product balance.

***p*-Benzoquinone (BQ) under Argon Atmosphere.** Following the general irradiation procedure, we irradiated 500 mg (3.96 mmol) of pyranone **1** and 428 mg (3.96 mmol) of BQ in ca. 30 mL of CCl_4 for 5.3 h. Flash chromatography with CH_2Cl_2/petroleum ether/ethyl acetate (5:5:3) as eluant gave the following fractions: 26.3 mg (0.206 mmol) of pyranone **1**, 51.0 mg (0.148 mmol) of aldehyde **6-BQ** (R_f 0.71), and 331 mg (1.41 mmol) of oxetane **2-BQ** (R_f 0.52), in that order.

Aldehyde 6-BQ: colorless powder; mp 148–150 °C (CH_2Cl_2/petroleum ether, 1:1); IR ($CDCl_3$) 3600, 3350–3200, 2970, 2810, 2740, 1770, 1685, 1600, 1520, 1230, 1160, 1025, 1000, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) (the carbon atoms of the aromatic ring are labeled with a prime for differentiation) δ 0.73 (s, 3 H, C*H*$_3$), 1.25 (s, 3 H, C*H*$_3$), AB signal (δ_A 2.60, δ_B 2.48, J = 17.0 Hz, 2 H, 2-H), 5.15 (s, 1 H, C*H*), 6.20 (br s, 1 H, O*H*), 6.87 (centered multiplet (m_c), 2 H, aromatic H), 6.99 (m_c, 2 H, aromatic H), 7.11 (m_c, 2 H, aromatic H), 7.47 (br s, 1 H, O*H*), 7.81 (m_c, 2 H, 2′,6′-H), 9.84 (s, 1 H, 4-H); ^{13}C NMR ($CDCl_3$, 50 MHz) (the carbon atoms of the aromatic ring are labeled with a prime for differentiation) δ 22.4 (q, *C*H$_3$), 25.4 (q, *C*H$_3$), 41.2 (s, C-3), 44.5 (t, C-2), 89.9 (d, *C*H), 115.3 (d), 116.0 (d), 126.8 (s, C-1′), 127.2 (d, C-3′,5′), 132.5 (d, C-2′,6′), 156.0 (s), 162.0 (s), 162.1 (s), 177.2 (s, C-1), 191.4 (d, C-4); MS (70 eV), *m*/*z* (relative intensity) 234 (0.3, M − hydroquinone), 206 (29, M − hydroquinone − CHO), 122 (75, $C_7H_6O_2^+$), 121 (79), 107 (3), 94 (2, $C_6H_5OH^+$), 93 (8, $C_6H_5O^+$), 77 (7), 65 (11), 56 (38).

Anal. Calcd for $C_{19}H_{20}O_6$ (344.4): C, 66.27; H, 5.85. Found: C, 66.36; H, 5.80.

Oxetane 2-BQ: colorless needles; mp 143–145 °C (2-propanol); IR ($CDCl_3$) 2970, 2930, 1760, 1670, 1630, 1160, 1110, 1060, 995, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 3 H, C*H*$_3$), 1.07 (s, 3 H, C*H*$_3$), AB signal (δ_A 3.00, δ_B 2.59, J = 17.7, $J_{4,6}$ = 2.2 Hz, 2 H, 4-H), 3.12 (dd, $J_{6,4}$ = 2.2, $J_{6,1}$ = 6.1 Hz, 1 H, 6-H), 6.25 (dd, J = 2.0, J = 10.1 Hz, 1 H, 3′-H or 5′-H), 6.27 (d, $J_{1,6}$ = 6.1 Hz, 1 H, 1-H), 6.34 (dd, J = 2.0, J = 10.5 Hz, 1 H, 3′-H or 5′-H), 7.16 (dd, J = 3.0, J = 10.1 Hz, 1 H, 2′-H or 6′-H), 7.26 (dd, J = 3.0, J = 10.5 Hz, 1 H, 2′-H or 6′-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.7 (q, *C*H$_3$), 29.8 (q, *C*H$_3$), 31.5 (s, C-5), 41.5 (t, C-4), 54.1 (d, C-6), 77.9 (s, C-7), 98.7 (d, C-1), 128.0 and 131.0 (2 d, C-3′,5′), 143.3 and 149.2 (2 d, C-2′,6′), 167.7 (s, C-3), 184.1 (s, C-4′); MS (70 eV), *m*/*z* (relative intensity) 234 (2, M^+), 206 (21, M − CO), 161 (8), 126 (28, $C_7H_{10}O_2^+$), 121 (100), 111 (30), 91 (15), 83 (37), 56 (54), 41 (51).

Anal. Calcd for $C_{13}H_{14}O_4$ (234.2): C, 66.66; H, 6.03. Found: C, 66.70; H, 6.33.

***p*-Benzoquinone (BQ) under Oxygen Atmosphere.** Following the general irradiation procedure, we irradiated 268 mg (2.12 mmol) of pyranone **1** and 230 mg (2.12 mmol) of BQ in ca. 30 mL of CCl_4 for 6 h. Flash chromatography with petroleum ether/CH_2Cl_2/ethyl acetate (8:5:1) as eluant gave the following fractions: 37.4 mg (0.140 mmol) of trioxane *cis*-**5**-BQ (R_f 0.29), 10.1 mg (0.038 mmol) of trioxane *cis*-**4**-BQ (R_f 0.25), 152 mg (0.571 mmol) of trioxane *trans*-**4**-BQ (R_f 0.21), and 146 mg (0.623 mmol) of oxetane **2**-BQ (R_f 0.15), in that order.

Trioxane *cis*-5-BQ: colorless needles; mp 110–111 °C (2-propanol); IR ($CDCl_3$) 2970, 2930, 1770, 1685, 1640, 1375, 1225, 1175, 1100, 1080, 1020, 855 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz, ca. 35 °C) δ 1.16 (s, 3 H, C*H*$_3$), 1.19 (s, 3 H, C*H*$_3$), AB signal (δ_A 2.71, δ_B 2.60, J = 17.9 Hz, 2 H, 9-H), 3.90 (d, $J_{1,6}$ = 8.3 Hz, 1 H, 1-H), 5.79 (d, $J_{6,1}$ = 8.3 Hz, 1 H, 6-H), 6.36 (m_c, 2 H, 3′,5′-H), 6.68 (m, 1 H, 2′-H or 6′-H), 7.38 (m, 1 H, 2′-H or 6′-H).

At −60 °C, a 33:67 ratio of two conformers was observed, but the individual resonances could not be assigned.

Major conformer: ^{1}H NMR ($CDCl_3$, 400 MHz, −60 °C) δ 1.15 (s, 3 H, C*H*$_3$), 1.23 (s, 3 H, C*H*$_3$), AB signal (δ_A 2.82, δ_B 2.68, J = 18.4 Hz, 2 H, 9-H), 3.99 (d, $J_{1,6}$ = 8.2 Hz, 1 H, 1-H), 5.85 (d, $J_{6,1}$ = 8.2 Hz, 1 H, 6-H), 6.42 (dd, J = 1.8, J = 10.6 Hz, 1 H, 3′-H or 5′-H), 6.45 (dd, J = 1.8, J = 10.2 Hz, 1 H, 3′-H or 5′-H), 6.62 (dd, J = 3.1, J = 10.2 Hz, 1 H, 2′-H or 6′-H), 7.73 (dd, J = 3.1, J = 10.6 Hz, 1 H, 2′-H or 6′-H).

Minor conformer: ^{1}H NMR ($CDCl_3$, 400 MHz, −60 °C) δ 1.20 (s, 3 H, C*H*$_3$), 1.30 (s, 3 H, C*H*$_3$), AB signal (δ_A 2.72, δ_B 2.64, J = 12.8 Hz, 2 H, 9-H), 3.94 (d, $J_{1,6}$ = 8.0 Hz, 1 H, 1-H), 5.89 (d, $J_{6,1}$ = 8.0 Hz, 1 H, 6-H), 6.37–6.46 (m_c, 2 H, 3′,5′-H), 6.78 (dd, J = 3.0, J = 10.2 Hz, 1 H, 2′-H or 6′-H), 7.16 (dd, J = 3.0, J = 10.4 Hz, 1 H, 2′-H or 6′-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.7 (q, *C*H$_3$), 27.3 (q, *C*H$_3$), 31.4 (s, C-10), 45.1 (t, C-9), 75.1 (d, C-1), 96.3 (s, C-3), 98.8 (d, C-6), 130.3 and 132.2 (2 d, C-3′,5′), 136.5 and 139.0

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(2 d, C-2′,6′), 165.5 (s, C-8), 184.1 (s, C-4′); MS (70 eV), m/z (relative intensity) 266 (2, M^+), 250 (1, M − O), 167 (2), 113 (43), 108 (85, BQ^+), 87 (55), 69 (29), 59 (68), 54 (100), 41 (86).

Anal. Calcd for $C_{13}H_{14}O_6$ (266.3): C, 58.64; H, 5.30. Found: C, 58.81; H, 5.43.

Trioxane *cis*-4-BQ, colorless needles, mp 111–112 °C (CH_2Cl_2/petroleum ether, 1:1), was obtained in pure form by preparative HPLC on silica gel with petroleum ether/ethyl acetate (1:1) at a flow rate of 27 mL/min (t_R = 4.3 min) and subsequent recrystallization: IR ($CDCl_3$) 2970, 2920, 2880, 1755, 1690, 1640, 1180, 1140, 1075, 1030, 975 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.16 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), AB signal (δ_A 2.61, δ_B 2.38, J = 18.4, $J_{8,6}$ = 1.2 Hz, 2 H, 8-H), 4.38 (dd, $J_{6,1}$ = 2.7, $J_{6,8}$ = 1.2 Hz, 1 H, 6-H), 5.82 (d, $J_{1,6}$ = 2.7 Hz, 1 H, 1-H), 6.26 (dd, J = 1.9, J = 10.2 Hz, 1 H, 3′-H or 5′-H), 6.36 (dd, J = 1.9, J = 10.5 Hz, 1 H, 3′-H or 5′-H), 6.60 (dd, J = 2.9, J = 10.2 Hz, 1 H, 2′-H or 6′-H), 7.13 (dd, J = 2.9, J = 10.5 Hz, 1 H, 2′-H or 6′-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.76 (q, CH_3), 24.84 (q, CH_3), 33.5 (s, C-7), 38.4 (t, C-8), 77.2 (d, C-6), 90.9 (s, C-3), 92.1 (d, C-1), 129.1 and 132.7 (2 d, C-3′,5′), 138.9 and 140.2 (2 d, C-2′,6′), 167.5 (s, C-9), 184.1 (s, C-4′); MS (70 eV), m/z (relative intensity) 266 (1, M^+), 250 (0.1, M − O), 124 (30), 113 (32), 108 (76, BQ^+), 87 (43), 82 (45), 80 (29), 59 (78), 54 (100).

Anal. Calcd for $C_{13}H_{14}O_6$ (266.3): C, 58.64; H, 5.30. Found: C, 58.39; H, 5.16.

Trioxane *trans*-4-BQ: thin colorless needles; mp 162–164 °C (2-propanol); IR ($CDCl_3$) 2970, 2940, 1765, 1690, 1640, 1465, 1400, 1380, 1180, 1155, 1085, 1070, 975 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.16 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), AB signal (δ_A 2.69, δ_B 2.63, J = 17.7 Hz, 2 H, 8-H), 4.19 (d, $J_{6,1}$ = 8.8 Hz, 1 H, 6-H), 5.82 (d, $J_{1,6}$ = 8.8 Hz, 1 H, 1-H), 6.34 (dd, J = 1.9, J = 10.6 Hz, 1 H, 3′-H or 5′-H), 6.38 (dd, J = 1.9, J = 10.2 Hz, 1 H, 3′-H or 5′-H), 6.59 (dd, J = 3.3, J = 10.2 Hz, 1 H, 2′-H or 6′-H), 7.50 (dd, J = 3.3, J = 10.6 Hz, 1 H, 2′-H or 6′-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (q, CH_3), 27.7 (q, CH_3), 32.3 (s, C-7), 45.3 (t, C-8), 85.6 (d, C-6), 90.8 (d, C-1), 96.9 (s, C-3), 129.4 and 133.0 (2 d, C-3′,5′), 137.1 and 138.2 (2 d, C-2′,6′), 165.5 (s, C-9), 183.8 (s, C-4′); MS (70 eV), m/z (relative intensity) 158 (0.2, M − BQ), 143 (0.2), 113 (14), 108 (62, BQ^+), 87 (28), 82 (26), 80 (21), 59 (57), 54 (100), 41 (70).

Anal. Calcd for $C_{13}H_{14}O_6$ (266.3): C, 58.64; H, 5.30. Found: C, 58.60; H, 5.14.

The X-ray structure of this compound is exhibited in Figure 1, and the data are available as supplementary material.

***o*-Phenanthraquinone (PQ) under Argon Atmosphere.** Following the general irradiation procedure, we irradiated 121 mg (0.961 mmol) of pyranone **1** and 200 mg (0.961 mmol) of PQ in ca. 20 mL of $CFCl_3$ at −5 °C for 2.3 h, resulting in 88% conversion. Flash chromatography with CH_2Cl_2 as eluant gave the following fractions: 14.5 mg (0.115 mmol) of pyranone **1** (R_f 0.44), 54.6 mg (0.164 mmol) of dihydrodioxin **6-PQ** (R_f 0.30), 24.0 mg (0.115 mmol) of PQ (R_f 0.22), 109 mg (0.326 mmol) of keto oxetane **3-PQ** (R_f 0.17), and 144 mg (0.431 mmol) of keto oxetane **2-PQ** (R_f 0.09), in that order.

Dihydrodioxin 6-PQ: colorless needles; mp 215–217 °C (ethanol); IR ($CDCl_3$) 3080, 2970, 2940, 1750, 1605, 1500, 1350, 1325, 1210, 1160, 1145, 1030, 1000 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), AB signal (δ_A 2.84, δ_B 2.45, J = 8.9 Hz, 2 H, 8-H), 4.04 (s, 1 H, 6-H), 6.28 (s, 1 H, 1-H), 7.60 (m_c, 4 H, 2′,3′,6′,7′-H), 8.13 (m_c, 2 H, 1′,8′-H), 8.60 (m_c, 2 H, 4′,5′-H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.9 (q, CH_3), 25.5 (q, CH_3), 33.3 (s, C-7), 38.8 (t, C-8), 73.3 (d, C-6), 92.8 (d, C-1), 120.5 (d), 120.8 (d), 122.5 (d), 122.7 (d), 125.3 (s), 125.5 (d), 125.7 (d), 126.8 (d), 127.0 (d), 127.1 (s) 127.4, (s) 129.4 (s), 132.3 (s), 168.4 (s, C-9); MS (70 eV), m/z (relative intensity) 334 (66, M^+), 210 (38), 209 (15), 208 (13, PQ^+), 181 (27), 180 (100, $C_{13}H_8O^+$), 111 (14), 83 (21), 69 (11), 55 (14).

Anal. Calcd for $C_{21}H_{18}O_4$ (334.4): C, 75.43; H, 5.43. Found: C, 75.60; H, 5.55.

Keto oxetane 3-PQ: colorless needles; mp 224–226 °C (2-propanol); IR ($CDCl_3$) 3080, 2970, 2930, 2880, 1750, 1700, 1600, 1450, 1265, 1190, 1175, 1120, 1000 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), AB signal (δ_A 3.14, δ_B 2.42, J = 17.0, $J_{4,6}$ = 1.7 Hz, 2 H, 4-H), AB signal (δ_A 5.12, δ_B 4.91, J = 5.3, $J_{6,4}$ = 1.7 Hz, 2 H, 6,1-H), 7.4–8.0 (m, 8 H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.0 (q, CH_3), 23.5 (q, CH_3), 33.1 (s, C-5), 40.0 (t, C-4), 78.5 and 79.5 (2 d, C-1,6), 92.2 (s, C-8), 123.7 (d), 125.3 (d), 126.5 (d), 127.5 (s), 127.8 (d), 128.8 (d), 129.9 (d), 130.9 (s), 131.2 (s), 135.4 (d), 137.5 (s), 168.0 (s, C-3), 196.6 (s, C-6′); MS (70 eV), m/z (relative intensity) 334 (27, M^+), 210 (24), 208 (10, PQ^+), 181 (24), 180 (100, $C_{13}H_8O^+$), 152 (32), 111 (16), 97 (11), 83 (21), 55 (14).

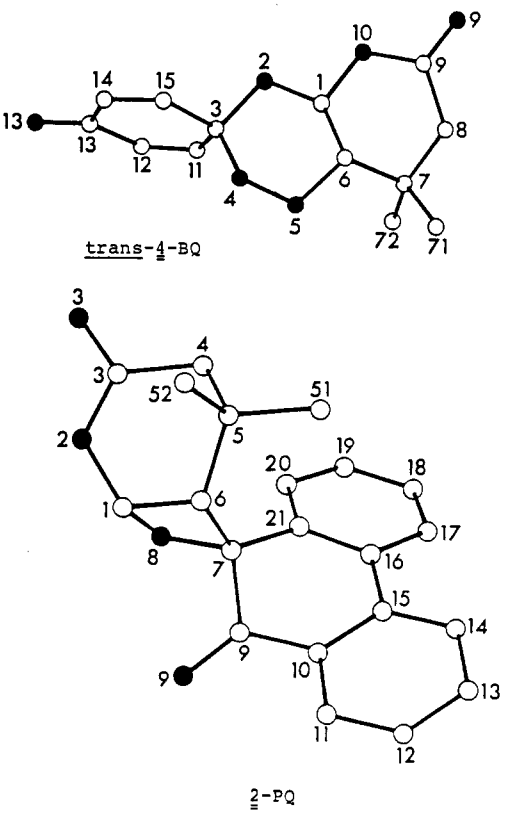

Figure 1. Perspective drawings of the oxetane **2-PQ** and 1,2,4-trioxane *trans*-**4-BQ**. The open and solid circles represent carbon and oxygen atoms, respectively, and their numbering refers to that of Tables I and II (see Supplementary Material Available paragraph at the end of this paper).

Anal. Calcd for $C_{21}H_{18}O_4$ (334.4): C, 75.43; H, 5.43. Found: C, 75.25; H, 5.36.

Keto oxetane 2-PQ: pale yellow prisms; mp 180–182 °C (2-propanol); IR ($CDCl_3$) 3080, 2970, 2940, 1760, 1705, 1600, 1450, 1260, 1170, 995, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.66 (s, 3 H, CH_3), 0.86 (s, 3 H, CH_3), AB signal (δ_A 2.90, δ_B 2.16, J = 17.3, $J_{4,6}$ = 2.3 Hz, 2 H, 4-H), 2.99 (dd, $J_{6,1}$ = 6.0, $J_{6,4}$ = 2.3 Hz, 1 H, 6-H), 6.41 (d, $J_{1,6}$ = 6.0 Hz, 1 H, 1-H), 7.4–8.0 (m, 8 H, aromatic H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.0 (q, CH_3), 30.0 (q, CH_3), 32.1 (s, C-5), 40.5 (t, C-4), 50.5 (d, C-6), 87.6 (s, C-7), 98.3 (d, C-1), 123.2 (d), 125.0 (d), 127.2 (s), 127.7 (d), 128.0 (d), 128.7 (d), 129.1 (d), 130.0 (d), 132.57 (s), 132.59 (s), 135.4 (d), 137.4 (s), 168.7 (s, C-3), 198.6 (s, C-6′); MS (70 eV), m/z (relative intensity) 334 (2, M^+), 234 (5), 208 (38, PQ^+), 181 (25), 180 (100, $C_{13}H_8O^+$), 152 (28), 151 (13), 111 (17), 83 (35), 55 (13).

Anal. Calcd for $C_{21}H_{18}O_4$ (334.4): C, 75.43; H, 5.43. Found: C, 75.30; H, 5.29.

The X-ray structure of this compound is exhibited in Figure 1, and the data are available as supplementary material.

***o*-Phenanthraquinone (PQ) under Oxygen Atmosphere.** Following the general irradiation procedure, we irradiated 121 mg (0.961 mmol) of pyranone **1** and 200 mg (0.961 mmol) of PQ in ca. 20 mL of $CFCl_3$ at −10 °C for 4 h, resulting in 90% conversion. Flash chromatography with CH_2Cl_2 as eluant gave the following fractions: 43.1 mg (0.129 mmol) of dihydrodioxin **6-PQ** (R_f 0.30), 20.0 mg (0.096 mmol) of PQ (R_f 0.22), 64.3 mg (0.192 mmol) of keto oxetane **3-PQ** (R_f 0.17), and 135 mg (0.404 mmol) of keto oxetane **2-PQ** (R_f 0.09), in that order.

Photostability Control Experiments. Separate solutions of 20.0 mg (59.8 μmol) of keto oxetanes **2-PQ** and **3-PQ** and 12.5 mg (59.8 μmol) of PQ and of dihydrodioxin **6-PQ** without PQ in ca. 2 mL of $CCl_4/CDCl_3$ (1:1) were irradiated with the laser light

for 1.8 h, 1.3 h, and 3.0 h, respectively, at −5 °C under an argon atmosphere. The reaction progress was monitored by TLC and/or ^{1}H NMR. Only keto oxetane **3**-PQ was photolabile under these conditions, affording significant amounts of dihydrodioxin **6**-PQ.

Acknowledgment. We are grateful to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for generous financial support. For spectral services we thank Dr. G. Lange (MS) and Dr. D. Scheutzow (NMR).

Registry No. **1**, 76897-39-7; **2**-BQ, 116053-49-7; (±)-**2**-PQ, 116053-56-6; **3**-BQ, 116053-53-3; **3**-PQ, 116053-55-5; (±)-*cis*-**4**-BQ, 116053-51-1; (±)-*trans*-**4**-BQ, 116053-52-2; (±)-*cis*-**5**-BQ, 116053-50-0; **6**-BQ, 116053-48-6; **6**-PQ, 116053-54-4; BQ, 106-51-4; PQ, 84-65-1; qinghaosu, 63968-64-9.

Supplementary Material Available: Tables of atomic coordinates and isotropic thermal parameters of **2**-PQ (Table I) and *trans*-**4**-BQ (Table II), bond angles (Table III), bond lengths (Table IV), and a crystallographic section (5 pages). Ordering information is given on any current masthead page.

Uncatalyzed and Chorismate Mutase Catalyzed Claisen Rearrangement of (*Z*)-9-Methylchorismic Acid

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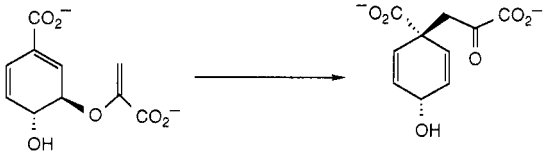
A synthesis of (−)- and (±)-(*Z*)-9-methylchorismic acid (**3**) is reported. The half-life for the uncatalyzed Claisen rearrangement of (±)-**3** in H_2O (pH 7.5, 30 °C) is 5.7 h. Chorismate analogue (−)-**3** was a modest substrate for chorismate mutase (chorismate mutase–prephenate dehydrogenase from *E. coli*): K_m = 4.0 mM, $k_{cat.}/k_{uncat.}$ = 4.2 × 10^4. It was established that the enzyme-catalyzed Claisen rearrangement of (−)-**3** proceeds through a chairlike transition state in similar fashion to the chorismate mutase catalyzed rearrangement of (−)-chorismic acid (**1**).

Chorismate (**1**) is the last common intermediate in the biosynthesis of aromatic amino acids and growth factors via the shikimate pathway in bacteria, fungi, and higher plants.[1] The first step in the biosynthesis of phenylalanine and tyrosine from **1** is the Claisen rearrangement to prephenate (**2**). The reaction is catalyzed by chorismate

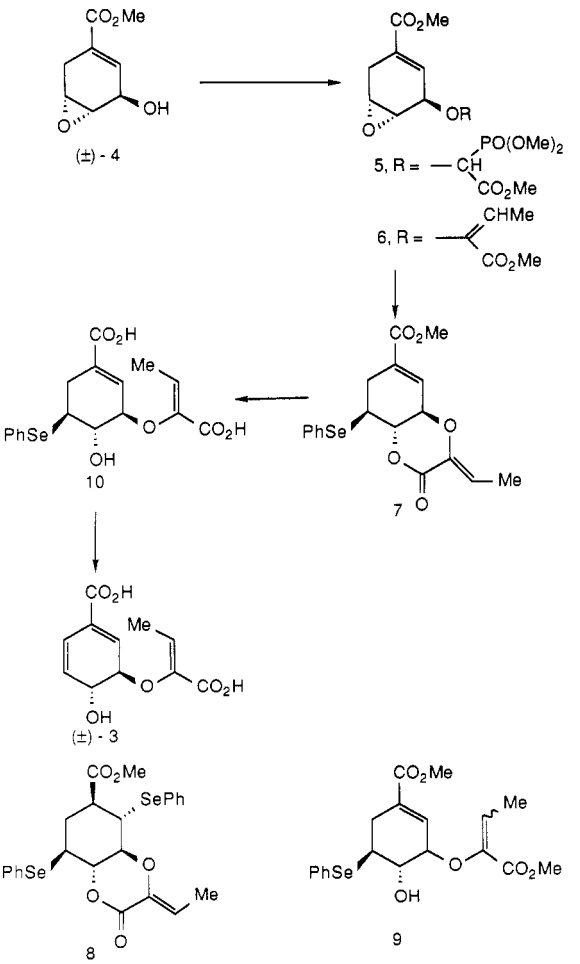


1 **2**

mutase. Recent investigations of labeled **1** with chorismate mutase–prephenate dehydrogenase from *Escherichia coli*[2] and with whole cells of *E. coli*[3] have established that the enzyme-catalyzed isomerization of **1** to **2** proceeds through a chairlike transition state. The uncatalyzed rearrangement of **1** to **2** also proceeds through a chairlike transition state.[4]

As part of our interest in structural features required in the substrate for catalysis of the Claisen rearrangement by chorismate mutase, we were interested in the (*Z*)-9- and (*E*)-9-methyl derivatives of **1**. Synthetic routes investigated provided (±)- and (−)-(*Z*)-9-methylchorismic acid (**3**), but the (*E*)-methyl isomer could not be obtained in sufficient purity for enzymatic studies. Described below are these synthetic investigations and studies of the thermal and chorismate mutase catalyzed Claisen rearrangement of (±)- and (−)-**3**.

Scheme I



The synthesis of (±)-**3** is outlined in Scheme I. The $Rh_2(OAc)_4$-catalyzed reaction of $MeO_2CC(N_2)PO(OMe)_2$ with (±)-**4**[5] gave a ~1:1 mixture of diastereomers **5**, which,

(1) For detailed reviews, see: (a) Weiss, U.; Edwards, J. M. *The Biosynthesis of Aromatic Compounds*; Wiley: New York, 1980. (b) Haslam, E. *The Shikimate Pathway*; Wiley: New York, 1974. (c) Ganem, B. *Tetrahedron* **1978**, *34*, 3353-3383.

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(3) Asano, Y.; Lee, J. J.; Shieh, T. L.; Spreafico, F.; Kowal, C.; Floss, H. G. *J. Am. Chem. Soc.* **1985**, *107*, 4314-4320.

(4) Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 5306-5308.

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