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Photochemical Rearrangements of Quinone Monoketals

Michael C. Pirrung* and David S. Nunn

Department of Chemistry, P. M. Gross Chemical Laboratory, Duke University, Durham, NC 27708-0346

Abstract: We have studied the photochemistry of over 15 quinone cyclic monoketals, which were prepared by diol exchange from the dimethyl ketals, Swenton oxidation/hydrolysis, or direct ketalization. Their reactions in acidic media are generally explained by the classical mechanism for cyclohexadienone photochemical (di-π-methane) rearrangements: photocyclization to a cyclopropane-oxyallylcation that is protonated, followed by solvolysis. This reaction pathway provides, after hydrolysis, β-carboxy-substituted cyclopentenones. With a substituent at the β-position of the quinone monoketal, rearrangement selectivity is modestly in favor of the more substituted alkene product. With a substituent at the α-position of the quinone monoketal, rearrangement selectivity is strongly in favor of the less substituted alkene product. Possible mechanistic reasoning to explain these observations is offered.

INTRODUCTION

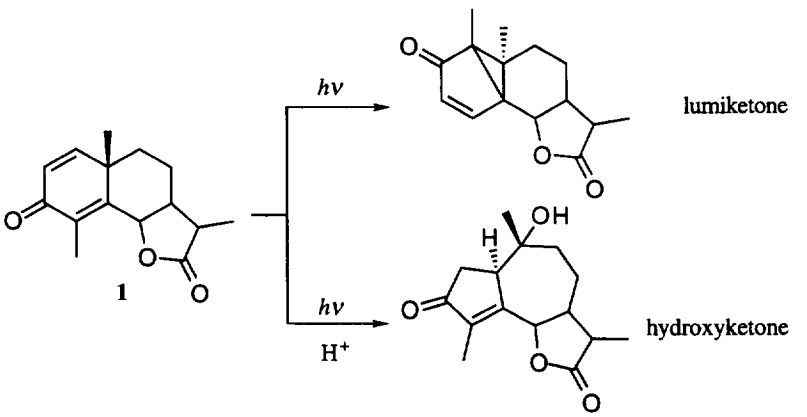
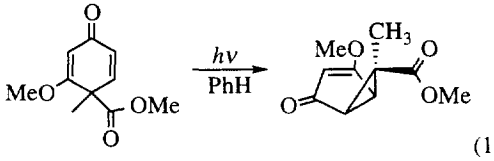


Figure 1: Cyclohexadienone Photochemistry

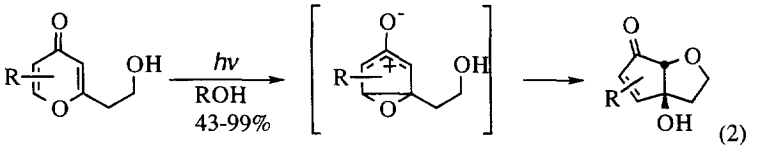
The photochemical rearrangement of cross-conjugated cyclohexadienones is one of the oldest known photoreactions. The photoreactivity of *α-santonin* (**1**), a prototype cyclohexadienone, was noted at the time of its isolation in 1830.[1] This reactivity was studied in Italy around the turn of the century, but the complexity of the structures involved, combined with the variety of products obtained under different irradiation conditions, prevented accurate characterization of the reaction.[2] Since the late 1950s the photochemistry of α-santonin and related cyclohexadienones has been the subject of intense study,[3] and many synthetic applications of the process are known. Earlier work has focused on the utility of the reaction in the synthesis of complex

polycyclic natural terpenes, and one important contributor to this literature has been Caine.[4] Most examples have involved photolysis under acidic conditions, giving rise to hydroxyketones or related structures (Fig 1). In this way the secondary photochemistry associated with lumiketones is avoided. The efficiency and stereoselectivity of the photoreaction make it a good strategy-level reaction, and the ready availability of 6/6-fused dienones and the efficiency of their photorearrangements makes them useful synthetic intermediates. They have been used as precursors in syntheses of natural products, such as (–)-cyclocolorenone, epicyclocolorenone, α-bulnesene, (+)-4-epiaromadendrene (–)-4-epiglobulol, and grayanotoxin II, possessing the common hydroazulene (5/7) ring system. They are also precursors in syntheses of (–)-axisonitrile-3, α-vetispirene, and β-vetivone, which possess the spiro[4.5]decane ring system.

The general utility in organic synthesis of the dienone photorearrangement has been limited because of the difficulty of accessing the required dienones, though some groups have derived monocyclic dienones from the plethora of available aromatic compounds. Efforts by Schultz[5] using dienones accessed via the reductive alkylation of benzoates have demonstrated useful levels of stereochemical control (Eq 1). Two heteroaromatic variations of the cyclohexadienone photorearrangement have been reported. γ-Pyranones bearing tethered hydroxyl groups undergo intramolecular trapping of a photogenerated zwitterion to give bicyclic systems (Eq 2).[6] γ-Silacyclohexadienones are converted to β–silylcyclopentenones, albeit in lower yields, in a process whose regioselectivity is explained via cleavage by solvent of an analogous photogenerated zwitterion.[7] Taveras has examined the photochemistry in methanol of a series of γ-methoxydienones and reports good yields of cyclopentenone-γ-ketals (Eq 3),[8] which could be formed by ring opening of a zwitterion. While cleavage of the three-membered ring of the zwitterion is otherwise common only in acidic media, the ability of the γ-alkoxy substituent to assist ring opening makes this hypothesis plausible.



(1)



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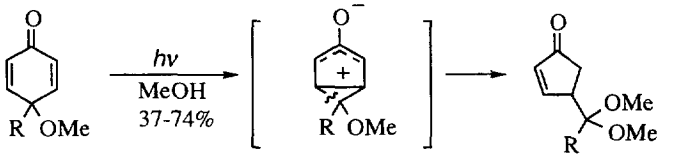
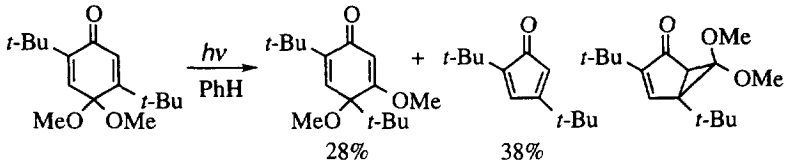


R = Me, Et, *i*-Pr, *t*-Bu

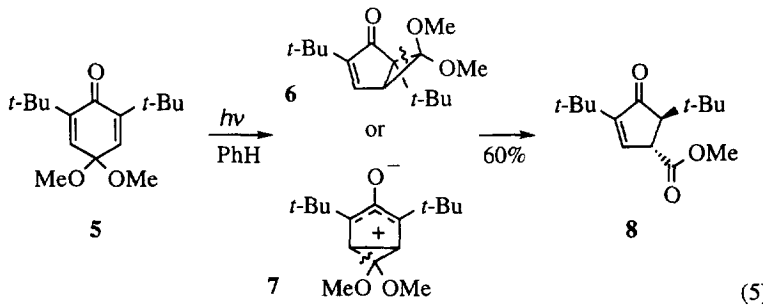
(3)

At the time this study began, there were only three reports on *p*-quinone monoketal photochemistry. Hewitt observed that quinone ketal **1** is converted to two identifiable products on irradiation in benzene with 366 nm light (Eq 4) and showed that **2** is a secondary photoproduct of lumiketone **4**.[9] The source of

cyclopentadiene **3** is not clear; Hewitt has proposed the extrusion of dimethoxycarbene from **4**, but was never able to determine the fate of this fragment. He also examined the photorearrangement of the isomeric 2,6-di-*t*-butyl compound **5**. In this case, cleavage of one of the bonds in the three-membered ring of lumiketone **6** or zwitterion **7** provided only the *trans* isomer of cyclopentenone **8** (Eq 5).

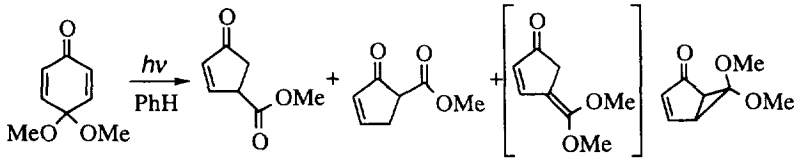


1 **2** **3** **4** (4)



5 **6** **7** **8** (5)

Margaretha has reported that the parent quinone ketal, **9**, is converted to cyclopentenones **10**, **11** (only 10-15% yield combined), and **12** (major, observed only by NMR) when irradiated in either benzene or *tert*-butanol at $\lambda > 370$ nm (Eq 6).[10] In water, only **10** was isolated, and the yield improved to 20-25%. The presence of **11** suggests at least some formation of the lumiketone **13**. The alternate isomer (**10**) could also be formed from **13**, or could be the product of cyclopropane bond cleavage in the zwitterion. Irradiation of the corresponding ethylene ketal under the same conditions permitted no products to be isolated, and NMR spectroscopy again suggested the formation of a ketene acetal.

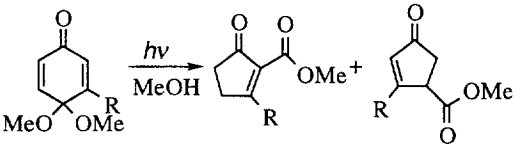


9 **10** **11** **12** **13** (6)

Feldman has demonstrated that β-substituted ketals **14** [R = CH_3 or 6-(5-hydroxy-2-methyl-1-cyclohexenyl)-3-hexenyl], when irradiated at 350 nm in methanol, provide a mixture of regioisomers **15** and **16** in moderate yield (Eq 7).[11] Orthoester precursors to the ester products could be observed by NMR spectroscopy of the crude reaction mixture, though these were hydrolyzed during workup. In hexane, benzene, acetonitrile, water, or 2-propanol, a complex reaction mixture resulted.

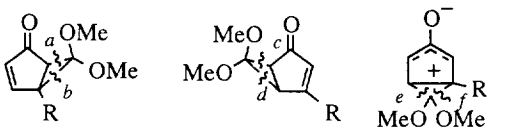
Isomer **15**, with the α-carbomethoxy group, most reasonably is formed from the lumiproduct **17**, while **16**, with the β-carbomethoxy group, could come from either lumiproduct **18** or directly from the zwitterionic

intermediate **19**. If both are formed from lumiproducts, cleavage of the bond to the α carbon would be required in one case, while cleavage of the bond to the β carbon would be required in the other case. That is, in both cases the cleavage must be completely regiospecific, though in the opposite sense. If **16** were known to be formed from the zwitterion, both products could be explained through cleavage of the more substituted bond of a cyclopropane intermediate.



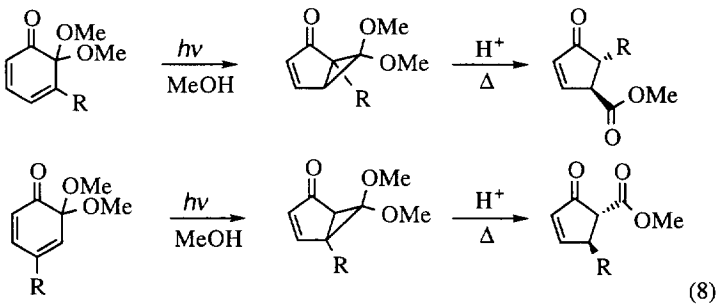
28% 33%

14 **15** **16**



17 **18** **19** (7)

The photorearrangement of *o*-quinone monoketals has also been communicated (Eq 8).[12] The dimethyl ketals, when irradiated in either MeOH or CF_3CH_2OH at 350 nm, gave rise to lumiketones, which were observed by ^1H NMR but not isolated. In refluxing TsOH/MeOH, they give cyclopentenones (30-80%). The regioselectivity observed with the dimethyl ketals, cleavage of the *more* substituted bond of the three-membered ring, was lost with other ketals; the *trans* stereoisomer was observed in all cases.



(8)

Although these reports were less than inspiring, efforts began in our laboratory to develop new synthetic methodology based on this reaction, exploiting the readily-available quinone monoketals.[13] Clearly the difficulty would lie in selectively directing reactive intermediates to divergent reaction pathways. With a simple β-substituted quinone ketal, four different carboalkoxycyclopentenones can be envisioned. If all possible stereoisomers and C=C tautomers are considered, at least twenty compounds are possible. With some substitution patterns the number is even higher. We reasoned, however, that the unshared pairs on the ketal oxygens could assist ring opening at the stage of the zwitterionic intermediate, short-circuiting the reaction pathway before it reached the lumiproducts and their various possible secondary photoproducts. Furthermore, previous work (see Discussion) suggested that α and β substituents on the dienone could control other aspects

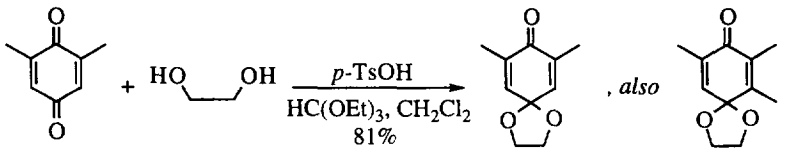
of reaction selectivity. The success of our study would hinge on the ability to find the correct combination of quinone ketal and reaction conditions to navigate a narrow path.

RESULTS

Preparation of quinone ketals[14]

In his review of quinone ketals,[15] Swenton lists three routes for their preparation: hydrolysis of quinone bisketals (in turn available *via* electrochemical oxidation of 1,4-dialkoxyaromatic systems); chemical oxidation of phenols; and electrochemical oxidation of phenols. Initial studies were performed using commercially available 4,4-dimethoxy-2,5-cyclohexadien-1-one (**9**).[16] All further studies were performed using quinone ketals synthesized by one of four methods.

Direct Ketalization. Unlike most ketones, quinones cannot generally be treated with an alcohol and catalytic acid to provide the ketal. At room temperature, no reaction occurs. With more forcing conditions, 1,4-addition or reduction, followed by irreversible aromatization, is observed. However, a ketalization strategy has been successfully applied by Sakaino to 2,6-dimethylbenzoquinone using ethylene glycol, *p*-toluenesulfonic acid (TsOH), and triethyl orthoformate (Eq 9).[17]. In our hands, this method suffered from a long reaction time (7-18 d, RT), but was easy to perform on a multigram scale and proceeded in essentially quantitative yield, based on recovered starting material. We made no attempts to increase the rate of the reaction by increasing the temperature; Sakaino, however, reports that at 80 °C the yield is reduced to 34%.

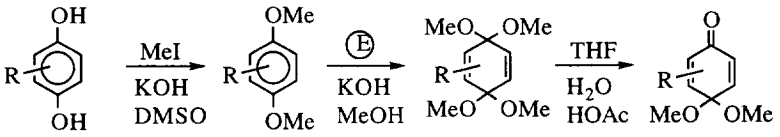


20 **21** (9)

The corresponding trimethyl compound **21** was also prepared in this manner (83% yield). In both instances, only ketalization of the less hindered carbonyl was observed; none of the alternate regioisomer or the bisketal was detected. This method allowed easy access to regioisomers that otherwise would have required multistep, protection/deprotection strategies (*vide infra*). Attempts to use this strategy with benzoquinone, 2,3-dimethylbenzoquinone, 2,5-diphenylbenzoquinone, or duroquinone did not provide any of the desired ketals. Thus, alkyl substituents are necessary to activate the system, and the quinone must be minimally 2,6-disubstituted, but may be maximally 2,3,5-trisubstituted. Neither ethanedithiol, 1,3-propanedithiol, mercaptoethanol, nor diethyl tartrate was found to substitute for ethylene glycol in reactions with either 2,6-dimethylbenzoquinone or 2,3,5-trimethylbenzoquinone.

Hydrolysis of Quinone Bisketals. The most general route to quinone ketals is the monohydrolysis of quinone bisketals, which are in turn available *via* electrochemical oxidation of hydroquinone bisethers. The vast library of available aromatic compounds and the wide range of aromatic substitution reactions are available to provide functionalized starting materials for this route.

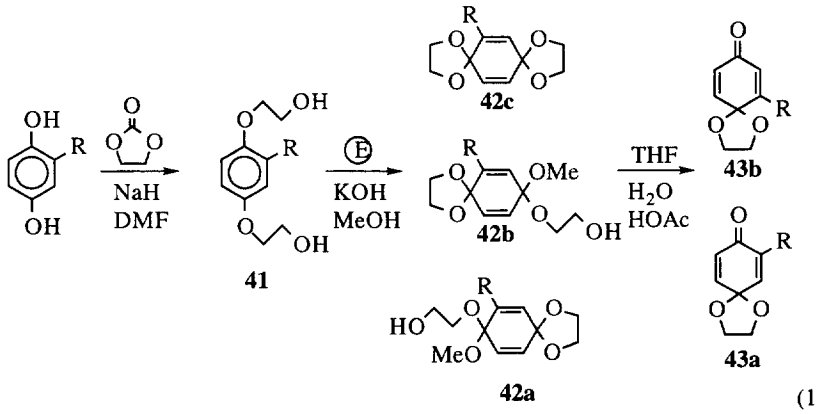
Dimethyl quinone ketals can be prepared in a three-step sequence from the corresponding hydroquinone: methylation to give the dimethoxybenzene; electrochemical oxidation; and monohydrolysis; as developed by Swenton (Eq 10).[15] The electrochemistry is easy to perform on a preparative scale in an undivided cell (i.e., a simple beaker or three-neck flask) using a carbon fiber anode and a nickel foil cathode. Methanol was the solvent, with 1-2% potassium hydroxide as supporting electrolyte. A constant current of ~0.5 A was applied until conversion of starting material was complete.



40 (10)

The hydrolysis of the bisketal (THF/H_2O/HOAc, room temperature) occurs much faster than the monoketal, permitting generation of the former in high yield. With substituted ring systems, the possibility of regioisomeric products arises. It is generally observed that the more sterically-hindered or electronically-deactivated ketal is preserved in the monoketal product. The methyl-substituted bisketal provided a 1:5 mixture of the α- and β-substituted monoketals **22** and **23**, respectively, while the trimethylsilyl compounds **25** and **26** were formed in a 1.5:1 ratio (Table 1). The α- and β-regioisomers can generally be separated by careful chromatography. The methoxy-substituted bisketal provided solely the β-substituted regioisomer, **27**. Compounds **22-27**, excepting **24**, have been synthesized before by this method.[18]

The ethylene ketals **29-39** (Table 1) were also prepared in a three step sequence from the corresponding hydroquinone (Eq 11). Alkylation was conducted with ethylene carbonate to give the bis(2-hydroxyethyl) ethers (**41**).[19] These desirable synthetic intermediates are almost all crystalline, allowing easy purification on a multigram scale. Yields for this reaction were typically 60-90%, excepting tetrafluorohydroquinone, which could not be alkylated under these conditions.

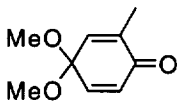
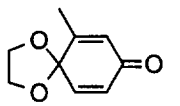
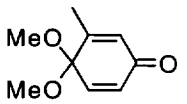
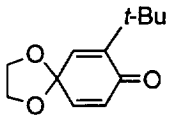
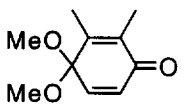
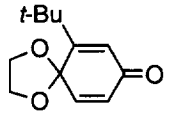
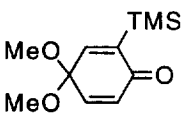
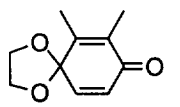
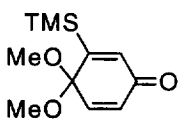
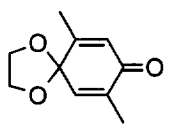
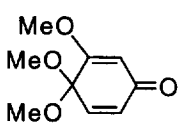
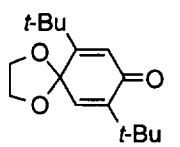
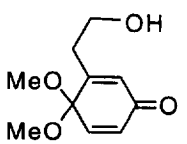
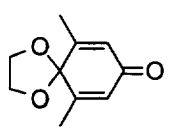
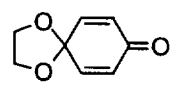
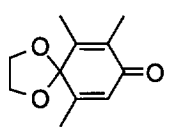
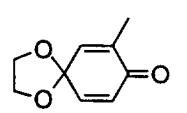
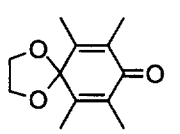


(11)

Electrochemical oxidation generally provided a mixture of the bisketals **42a** and **42b** along with dispiro ketal **42c**. These were not separated, but hydrolyzed directly to the monoketal(s) **43a/43b**. Unlike the tetramethyl bisketals, the more robust ethylene bisketals were hydrolyzed at reflux temperature. A total of

eleven ethylene ketals were prepared by this method (Table 1). Except for **28** and **29**,[20] these compounds are previously unreported.

Table 1: Synthesis of Quinone Ketals by Bisketal Hydrolysis

Cpd #	Structure	Yield* (%)	Cpd #	Structure	Yield* (%)
22		12†	**31**		46§
23		60†	**32**		27¶
24		57	**33**		29¶
25		30‡	**34**		77
26		21‡	**35**		44
27		58¥	**36**		51
28		65	**37**		41
29		76	**38**		66
30		20§	**39**		27

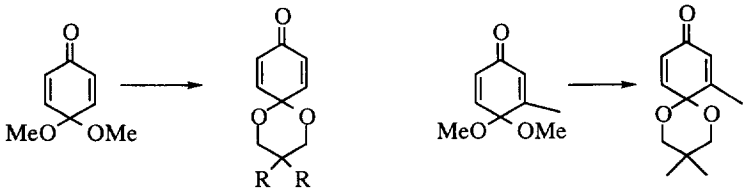
* Isolated yield for the three step sequence: alkylation, oxidation, hydrolysis.

¥ Isolated yield for the two step sequence: oxidation, hydrolysis.

†,‡,§,¶ Pairs of products formed from common bisketal precursor.

The regioselectivity of hydrolysis for this sequence is similar to the observations above, but is somewhat more complex. When dispiro ketal **42c** (R = CH_3) was isolated from the oxidation mixture and subjected to hydrolysis, a 1:15 ratio of isomers **43a**:**43b** was observed (GC, ^{1}H NMR). This is in contrast to a 1:2 ratio (**43a**:**43b**) for hydrolysis of the crude electrolysis product. A possible explanation is that the oxidation to form **42a** and **42b** is non-selective, while the hydrolysis step is completely selective in that **42a** produces **43a**, while **42b** produces **43b**. The more rapid hydrolysis of the acyclic ketal is well precedented and has been rationalized based on stereoelectronic effects.[20b] The final product ratio would depend on the ratio of (**42c** + **42b**):**42a**. This rationale explains why the *tert*-butyl group, which should be a strong directing group based both on its steric demands and its inductive power, provided only a 1:1 mixture of isomers **32** and **33** and suggests that a more efficient synthesis of **43b** should be available by converting **42a** and **42b** to **42c** (TsOH/ether)[21] before performing the hydrolysis.

We have reported another method, diol exchange, to obtain quinone monoketals.[22] As described in our preliminary communication and in the Experimental Section, subjection of the readily-available dimethyl ketals to boron trifluoride etherate and a diol in DME produces in excellent yield the corresponding cyclic ketals (Eq 12). The photochemistry of three of the compounds prepared by this method, **44**-**46**, has been studied.

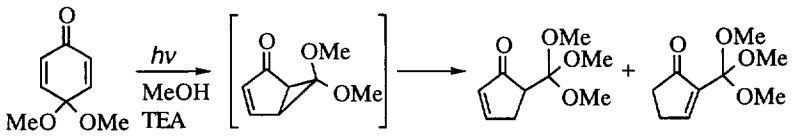


44 R = H
45 R = Me

46 (12)

Through the complementary methods of electrochemical oxidation/hydrolysis and direct ketalization, all possible substitution patterns of methyl groups on the dienone ring of quinone monoketals have been accessed. Monoketals bearing a number of other substituents were prepared. A few cyclic ketals were synthesized by our exchange procedure, and a total of eighteen different quinone ketals were ultimately prepared for photochemical study.

Photochemistry



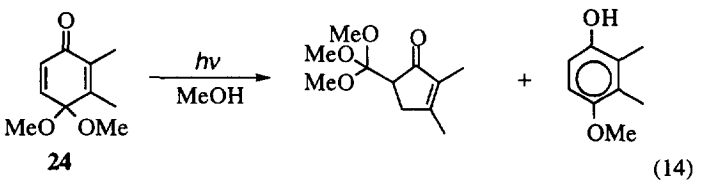
9 **13** **47** **48** (13)

Dimethyl Ketals. We began our studies using the simplest quinone ketal, **9**. To prevent simple hydrolysis of the ketal, a small amount (~25 mM) of triethylamine (TEA) was added to the reaction mixture, a technique that had also been employed by Feldman. Schuster has studied the photochemical electron transfer

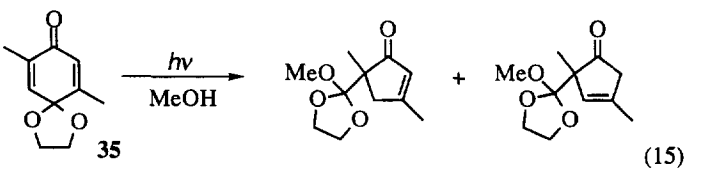
reaction of cyclohexadienones in the presence of TEA.[23] Although that reaction gives phenol products, the amine was used as solvent, and as the concentration of amine was decreased, the yield of lumiketone increased. At the concentration of TEA we employed, no such electron transfer chemistry was expected, and indeed, it resulted in *decreased* formation of phenol. Irradiation at 350 nm of a solution of **9** in dry methanol allowed the isolation of orthoester **48** in 40% yield (Eq 13). The tautomeric **47** was also observed in the ^{1}H NMR spectrum of the crude reaction mixture, but evidently rearranged during isolation.

The structure of **48** was clear from its spectroscopic data. The ^{1}H NMR spectrum indicated that C-4 was trapped to yield an orthoester (δ 3.19, s, 9H). The UV spectrum (λ_{max} = 235 nm, log ε = 3.24) and IR carbonyl stretch (1708 cm^{-1}) confirmed the conjugated cyclopentenone structure. The ^{1}H NMR spectrum showed a single olefinic proton (δ 7.91, t, J = 2.7), the chemical shift of which identified it as the β proton of the cyclopentenone.[24] This established that the trimethoxymethyl group was attached at the α position of the enone. Furthermore, the orthoester hydrolyzed on prolonged standing in chloroform to give the methyl ester, identical with authentic material.[25] It is reasonable that products **47** and **48** are formed from lumiketone **13**.

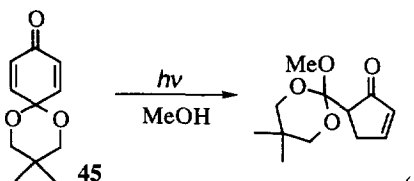
When **9** was irradiated at shorter wavelengths (254, 300 nm, MeOH), *p*-methoxyphenol became the principal product. Irradiating **9** in acetone, THF/MeOH, or CH_2Cl_2/MeOH resulted in increased amounts of phenol. In water, reductive dimerization was observed. No attempts were made at triplet sensitization, although other researchers have had success with this method. Reactions were also performed using various alcohols in the place of methanol, again with the addition of TEA. Using ethanol, isopropanol, 2-butanol, isobutanol, or *n*-butanol resulted in increased phenol formation. Little phenol formation was noted with *tert*-butanol, but more complex reaction mixtures were invariably observed using these higher alcohols. Similarly, reactions performed using benzene, CH_2Cl_2, CH_2Cl_2/MeOH, Et_2O/MeOH, or THF/MeOH, each in the presence of TEA, gave more complex reaction mixtures, as did elevated temperature. Cooling the reaction vessel in a dry ice/isopropanol bath allowed isolation of **48** in 75% yield.



24 (14)



35 (15)

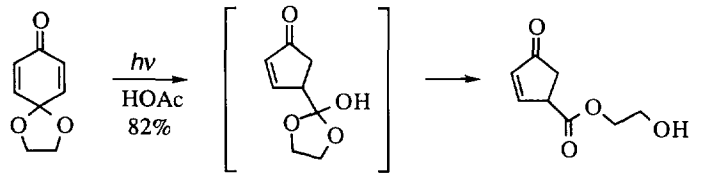


45 (16)

Optimized reaction conditions were applied to other quinone ketals. With benzoquinone ethylene ketal, phenol production was the result. However several other ketals were shown (^{1}H NMR) to give α-substituted orthoesters analogous to **48** (Eq 14-16).

We had initially anticipated that irradiation of quinone monoketals would proceed via bond cleavage at the zwitterion stage (**19**), with the two C-4 oxygens acting to stabilize the forming positive charge. Trapping of this intermediate with solvent (rather than intramolecular rearrangement to give the bicyclo[3.1.0]hexenone) would produce a cyclopentenone where the orthoester moiety was of necessity at the β position. However, our results clearly indicated that the lumiketone was being formed. In view of recurring difficulties with phenol formation and concerns about regiochemical control in the solvolytic cleavage of lumiketones, a strategic retreat was called for. With 4,4-dialkylcyclohexadienones, cleavage of the three-membered ring at the stage of the zwitterion is effected by performing the reaction in aqueous acetic acid. Unfortunately, the dimethyl ketals are too hydrolytically-labile for these conditions. To test this strategy for directing the carboalkoxy group to the β position, we therefore turned our attention to the more hydrolytically stable ethylene ketals.

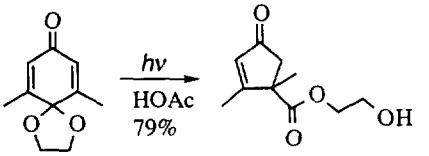
Ethylene Ketals. The stability of the ethylene ketal **29** toward acid was first tested. Little hydrolysis was observed in glacial acetic acid or 50% methanolic acetic acid (room temperature or reflux). Concluding that the ketal ring was sufficiently robust that photolysis would occur faster than hydrolysis, glacial acetic acid was chosen as the solvent, and **29** was irradiated with light of $\lambda \geq 350$ nm. Cyclopentenone **49** was isolated in good yield (Eq 17). Again, its structure followed readily from the spectral data. The two signals in the olefinic region of the ^{1}H NMR spectrum (δ 6.29, dd, J = 5.6, 2.4 and δ 7.71, dd, J = 5.6, 2.8) clearly represent the α and β protons of the cyclopentenone. The small coupling constant is in each case due to coupling to the methine proton (δ 3.95, m), which is vicinal to the β proton and allylic to the α proton. The diastereotopic protons of the methylene in the ring are observed at δ 2.79 (dd, J = 18.9, 2.8) and δ 2.64 (dd, J = 18.9, 7.1), the large geminal coupling constant being particularly diagnostic of a cyclopentanone. Signals for the methylenes of the hydroxyethyl side chain are observed at δ 3.87 and δ 4.28. The IR stretch at 1705 cm^{-1} accounts for both the ester carbonyl and the cyclopentenone. The hydroxyethyl ester moiety is the expected rearrangement product of the hydroxydioxolane, formed by trapping of adventitious water.[26]



29 **49** (17)

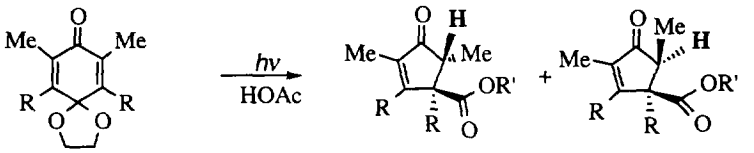
A second test of this reaction selectivity involved the irradiation of the dimethyl substituted ketal **37** (Eq 18). Again, a single isomer was isolated, identified as **50**. The structure follows readily from the ^{1}H NMR data, which clearly shows one olefinic proton, α to the carbonyl, and a methylene bearing diastereotopic protons. With this compound, the ester (1725 cm^{-1}) and cyclopentenone (1690 cm^{-1}) IR stretches were clearly resolved. The ready formation of a quaternary center in this reaction is noteworthy.

The results of these two experiments, that irradiation of quinone ethylene ketals in glacial acetic acid results in formation of a cyclopentenone with a carboalkoxy group in the β position, have been found to be quite general. In all the ethylene ketals studied (*vide infra*), only the products of this mode of reactivity have been identified from photolyses in acetic acid. We believe that this "β selectivity" is enforced by the acidic reaction conditions, and that the products are formed directly from the zwitterion, rather than by breakdown of the lumiketone.



37 **50** (18)

The above two experiments were presented first because their symmetry clearly shows the α vs. β selectivity of the reaction without the necessity to address other questions of regio- and stereoselectivity. The following two experiments were chosen to address a stereochemical question: Assuming that β selectivity is operational, substrates such as **20** and **39** could be expected to give a mixture of *cis* and *trans* isomers (Eq 19). In the event, irradiation of **20** provided an 11:1 mixture of epimers (79% yield), while **39** provided a 1.3:1 mixture (81% yield). These diastereomers were not separable by flash chromatography.

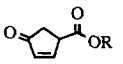
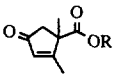
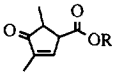
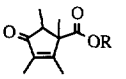
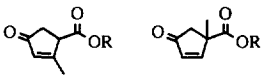
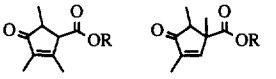
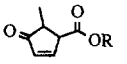
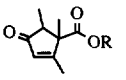
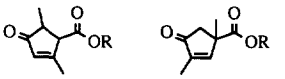
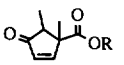


20 R = H **51a** R = H **51b** R = H
39 R = Me **52a** R = Me **52b** R = Me (19)

The assignment of stereochemistry was based on ^{1}H NMR spectral data. The spectra of the pairs of epimers differed most significantly in the chemical shift of the emboldened methine proton. The difference in chemical shifts, Δδ, was ~0.5 ppm. The methine proton in epimer **a** is *cis* to the carboalkoxy group, and thus is expected to be deshielded by the carbonyl. In the alternate epimer **b**, no such deshielding is possible, and a normal shift is predicted. On these grounds we conclude that the major diastereomer in each case, showing δ ~2.8, was isomer **a**. This assignment was corroborated with difference NOE experiments on compounds **51a** and **52a,b** (Fig 2). In epimer **51a** (major), irradiation of the α methyl group (δ 1.29) resulted in clear enhancement of the β methine signal (δ 3.35), indicating that this α methyl group was *cis* to the methine proton. Epimer **51b** was present in insufficient quantities to obtain accurate NOE data. In epimer **52a** (major), irradiation of the quaternary methyl group (δ 1.31) generated a small enhancement in the signal of the α-methyl group (δ 1.19). In contrast, with the minor epimer **52b**, irradiation of the quaternary methyl (δ 1.48) resulted in significant enhancement of the α-methine signal (δ 2.82). Thus the α-methine proton of the major epimer (**52a**) is *cis* to the carboalkoxy group and has a greater downfield shift than the α-methine of the minor

epimer **52b** (δ 2.82 vs. δ 2.27). Based on these observations, the stereochemistry for each cyclopentenone synthesized in this study was assigned.

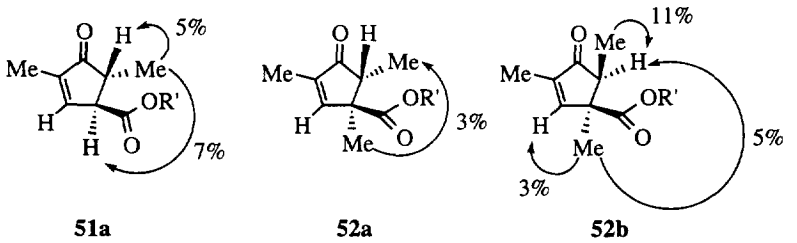
Table 2: Photochemical Results

Dienone		Photoproduct(s)	Ratio of Epimers	Yield (%)*
29		**49** 	–	82
37		**50** 	–	79
20		**51** 	1:1	78
39		**52** 	1.3:1	81
31		**53/54** 	–	44 + 23
21		**55/56** 	>11:1 2.6:1	39 + 35
30		**57** 	10:1	79
38		**58** 	3:2	84
35		**59/60** 	7:1	48 + <1
34		**61** 	2:1	89

R = CH_2CH_2OH

* isolated yields

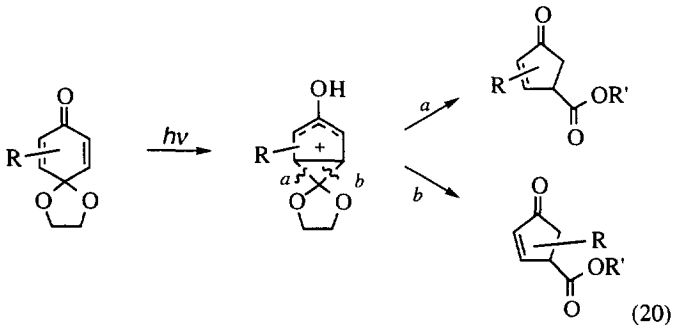
In all reactions where diastereoselectivity is possible, the major diastereomer observed was the one resulting from protonation on the same face of the ring as the carboalkoxy side chain. This selectivity is in the same sense, but to a much lesser degree, as that observed by Hewitt and Liao (eq 5). It is not clear if the steric bulk of their substituents are responsible for this result. It was not determined whether these values reflect a kinetic, alkyl-controlled protonation in acetic acid, or whether equilibration is possible under the reaction conditions. The stereoselectivity results are summarized in Table 2.

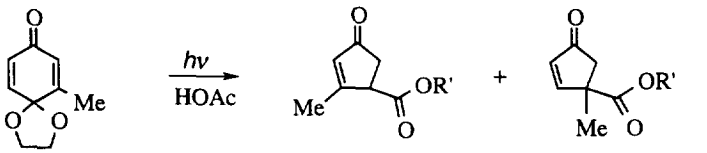


51a **52a** **52b**

Figure 2: NOE Difference Experiments

In the above four reactions, the ketal ring lies within a plane of molecular symmetry. A remaining question of selectivity in this reaction is only observable when the ketal ring does *not* lie in a plane of symmetry. That is, with a substituent on the dienone ring, will bond cleavage occur to give the more substituted double bond (path *a*, Eq 20) or the less substituted double bond (path *b*)? The answer to this question may depend not only on the nature of R, but also on the position of R (α vs. β) on the dienone ring.



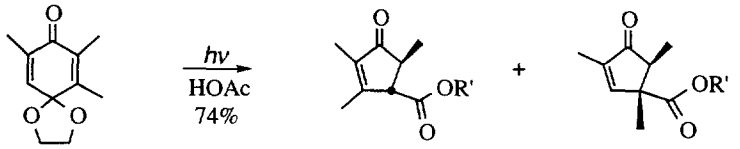


31 **53** **54** (21)

Examining first the case where the cyclohexadienone ring is unsymmetrically substituted at the β position, we had two probes for this type of selectivity. Compound **31**, when irradiated in acetic acid, provided a 2:1 mixture of compounds **53** and **54** in a combined yield of 67% (Eq 21). These compounds were

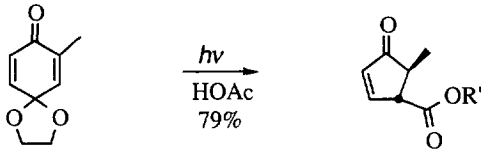
separable by flash chromatography. Their structures follow readily from their spectroscopic data. Thus the selectivity for producing the carboalkoxy group in the β position remained, but only a slight preference for breaking the *more* substituted bond of the three-membered ring was observed.

Irradiation of **21** provided a 1.1:1 mixture of isomers **55** and **56**, this time in a combined yield of 74%, and again favoring very slightly the cleavage of the *more* substituted bond in the zwitterion (Eq 22). The regioisomers were partially resolved by flash chromatography. Compound **56** was isolated as a 2.6:1 mixture of epimers (major indicated). Only one epimer of **55** could be identified.



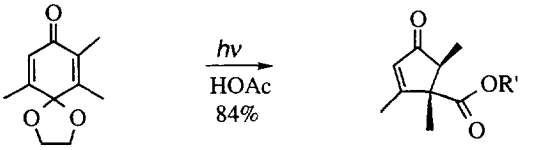
21 **55** **56** (22)

Two molecules are also available to probe for selectivity in the case where the cyclohexadienone ring is unsymmetrically substituted at the α position. Compound **30**, when irradiated in acetic acid, provided **57** in a 79% yield (Eq 23). This compound was isolated as a 10:1 mixture of epimers (major epimer shown).



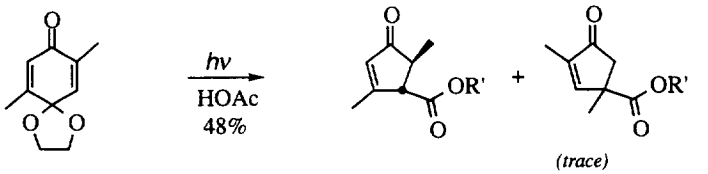
30 **57** (23)

The preference for the α substituent to be located on an sp^3-hybridized ring carbon so as to give a cyclopentanone with a *less* substituted double bond is reiterated in the reaction of **38** to give **58** (Eq 24). Only one regioisomer was isolated, in an 84% yield. ^1H NMR spectroscopy indicated that **58** was a 3:2 mixture of epimers (major epimer shown).



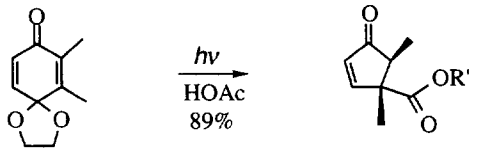
38 **58** (24)

There remain two substitution patterns to be discussed. In these, substituents are positioned so that both α directing and β directing effects can be observed. In the irradiation of **35**, our earlier results suggest that the preference for cleavage of the more substituted bond of the zwitterion should be supported by the preference for the α substituent to be located on an sp^3 carbon. The predicted isomer **59** is in fact the major product, being formed in 48% yield, as a 7:1 mixture of epimers (Eq 25). Traces (< 1%) of a second isomer, tentatively assigned structure **60**, were seen in ^1H NMR spectra.



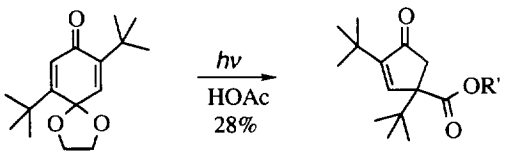
35 **59** **60** (25)

In the irradiation of **34**, however, our model suggests that the preference for cleavage of the more substituted bond of the three-membered ring will be opposed by the preference for the α substituent to be on the sp^3 carbon. In the event, only isomer **61** (2:1 mixture of epimers), with the less substituted double bond, was formed (Eq 26). The α substituent must therefore play the dominant role in determining this type of selectivity.

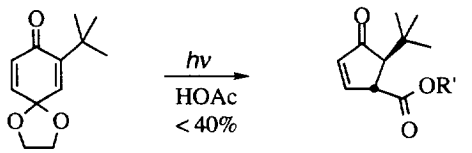


34 **61** (26)

The above examples represent all ten possible substitution patterns of one to four methyl groups on the cyclohexadienone ring. The selectivity patterns probed include carboalkoxy group α vs. β (β strongly preferred), *cis* vs. *trans* stereochemistry (*trans* moderately preferred), cleavage of the more vs. the less substituted cyclopropane bond in the zwitterion intermediate (cleavage of more substituted bond slightly preferred), and more vs. less substituted double bond formed (α substituent preferred on sp^3 carbon). These results are summarized in Table 2.



36 **62** (27)



32 **63** (28)

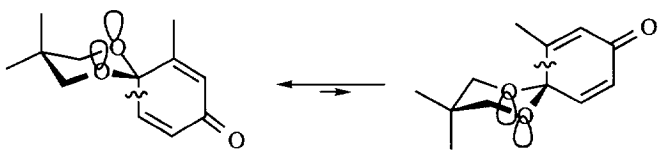
The photolyses of several ethylene ketals bearing substituents other than methyl were also examined. The *t*-butyl-substituted compounds **36** and **32** gave significantly more complex reaction mixtures than did the methyl-substituted compounds, thus hindering reaction characterization. From **36**, the only product that could be clearly identified was **62**, which was isolated in only 28% yield (Eq 27). This product, which contains

three quaternary centers, is formed through selectivity opposite to that observed for the similarly substituted **35** (Eq 25), though the low isolated yield makes it difficult to draw generalities from this result. The α-*t*-butyl-substituted **32** provided cyclopentenone **63** as the principal product (Eq 28). Here the selectivity is in keeping with the previous examples.

When the β-methoxy substituted ketal **27** was irradiated, only a slow degradation of starting material was observed. No products could be identified in the ^{1}H NMR spectrum of the crude reaction mixture. While efficient photorearrangements of cyclohexadienones bearing α-methoxy or β-methoxy groups have been previously demonstrated, Schultz has also noted the ability of the methoxy substituent to inhibit cyclopentenone formation.

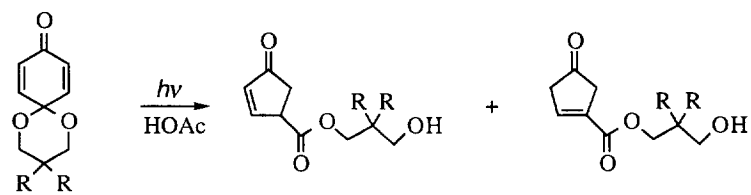
The crude reaction mixture resulting from irradiation of α-trimethylsilyl-substituted ketal **34** showed ^{1}H NMR signals characteristic of a β-carboalkoxycyclopentenone, but decomposition occurred during chromatography, and only the protiodesilylation product **49** was isolated.

Other Spiroketals. The exchange ketalization technique allowed access to a variety of ketal types. We had developed the technique to allow the comparison of reactivity of different ketal ring types in the photoreaction. One aim through such a change was to use stereoelectronic effects to control the bond cleavage process. A first approach was to modify the ring size to 6 members in compound **46**. Two chair forms of **46** are pictured (Fig 3). Molecular mechanics calculations indicate a strong bias (4.5 kcal/mol) for form **46a**.[27] Each conformer has two oxygen lone pairs *anti*-periplanar to one bond (indicated) in the dienone ring. Expecting significant lone pair participation in bond breaking, we postulated that the conformational bias for **46a** would translate to a strong preference for cleavage of the *less* substituted bond during the photorearrangement. With ethylene ketals, a very slight preference for cleavage of the *more* substituted bond was observed. Thus switching ketal types might allow a reversal of this selectivity.



46a **46b**

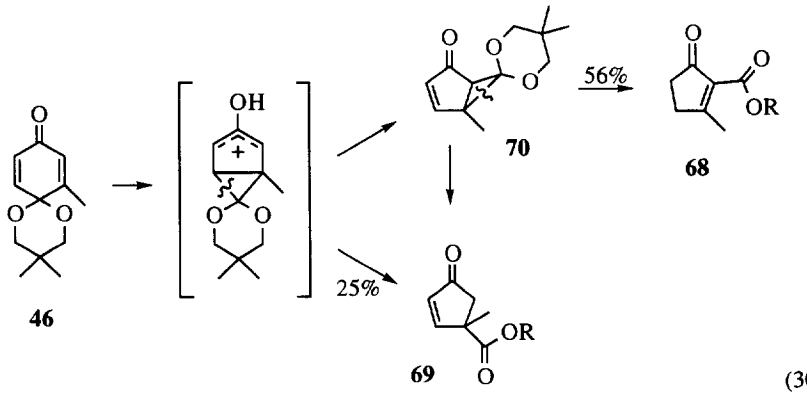
Figure 3: Conformational Equilibrium and Stereoelectronic Effects in **46**.



44 R = H	41%	**64**	17:1	**65**	
45 R = Me	35%	**66**	13:1	**67**	(29)

To test this hypothesis, the ketals **44** and **45** were irradiated, and it was confirmed that the isomers with the carboalkoxy group in the β position were formed (Eq 29). It appears that some of the tautomers **65** and **67** were also formed, but this assignment is tentative, as the compounds could not be separated chromatographically and evidence for their presence comes only from the ^{1}H NMR spectra. The lower yields observed reflect the moderate instability to isolation of unsubstituted cyclopentenones.

The β-methyl substituted ketal **46** was then irradiated. If our hypothesis were correct, the reaction would favor a product like **54**, in which the less substituted bond of the intermediate has been cleaved, at the expense of a product like **53** (Eq 21). In the event, exclusively the products of less substituted bond cleavage *were* observed, though not in the sense expected. Rather, a mixture of **68** and **69** was obtained in 81% combined yield (Eq 30) that could be separated by flash chromatography. Cyclopentenone **68** must come from lumiproduct **70**, rather than from solvent trapping of the zwitterion. This was the only instance in which we observed a product with the carboalkoxy group in the α position when using the acetic acid photolysis conditions.



(30)

Several explanations for the appearance of **68** are possible. One is that the [1,4] shift is more rapid than cleavage of the zwitterion for this substrate. The ratio of **68** to **69** would then reflect the preferential solvolysis of the more substituted bond of **70**. Alternatively, the lumiketone may be formed not through the classical concerted mechanism, but in a stepwise fashion, beginning with the cleavage of the indicated bond in the zwitterion. In this case **69** is formed by direct solvent trapping of the intermediate, while the lumiketone is formed by intramolecular trapping. The lumiketone could subsequently solvolyze to give **68** or a mixture of **68** and **69**. Intramolecular trapping may compete in this system because of the steric hindrance to solvent trapping caused by the nearby quaternary center.

DISCUSSION

The photochemical rearrangements of quinone monoketals reported above must be viewed in the context of the existing mechanistic framework for cyclohexadienone photochemistry. In 1961, Zimmerman and Schuster proposed the mechanism summarized in Fig 4.[28] The reaction is believed to occur through the $n\rightarrow\pi^*$ excited triplet state, as evidenced by the ability to use triplet sensitizers such as benzene (E_T = 85 kcal/mol) or benzophenone (E_T = 69 kcal/mol).[29,30,33] Furthermore, it is quenched by piperylene (E_T = 57-60 kcal/mol) or

1,3-cyclohexadiene (E_T = 54 kcal/mol).[31] The phosphorescence spectrum of cyclohexadienones has been recorded at 77 K, and the triplet energy thus measured is ~67 kcal/mol.[29,32] No fluorescence is observed, consistent with efficient intersystem crossing. The quantum yield for the reaction is high, typically 75-100%.[30a,33]

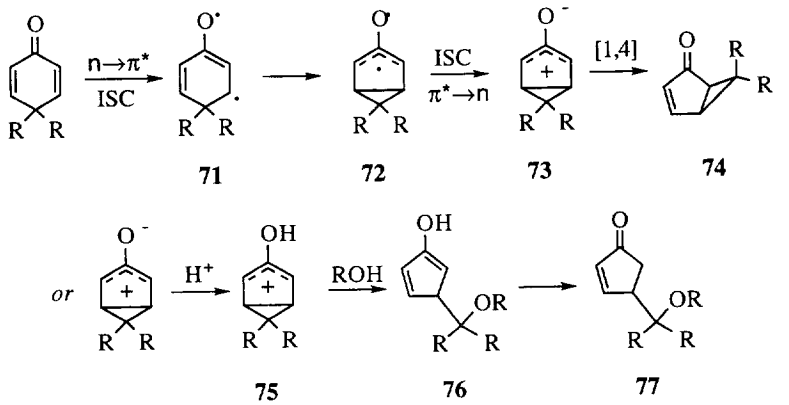
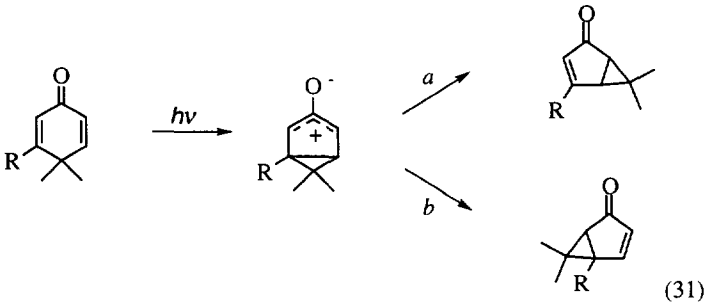


Figure 4: Zimmerman-Schuster Mechanism for Photochemical Rearrangements of Cyclohexadienones

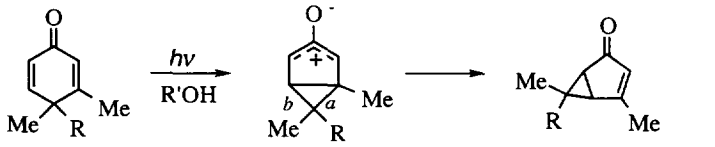
β-Bond formation in excited state **71** gives a bicyclo[3.1.0]hexane intermediate (**72**). Molecular orbital calculations by Zimmerman suggest that only the n→π* excited dienone shows increased bond order between C-3 and C-5 as would be required for β-bonding.[34] Intersystem crossing and nonradiative decay give a zwitterion (**73**). Zimmerman has provided support for zwitterionic intermediates by generating them via a non-photochemical route and demonstrating their rearrangement to lumiketones.[35] Additional evidence has come through experiments with dienones modified by an electronegative trichloromethyl group that disfavors subsequent steps and, in the presence of HCl, allows trapping by solvent.[36] Matoba has shown that zwitterions generated from α-methoxydienones are readily trapped by methanol to give acetals.[37] In addition to trapping by simple nucleophiles, the zwitterion is subject to electrocyclic trapping by furan and cyclopentadiene.[38] The fate of the zwitterion **73** in neutral solvents, typically dioxane or benzene, is sigmatropic shift to give the bicyclo[3.1.0]hexenone (**74**), often referred to as a *lumiketone* or simply a *lumiproduct*. The fate of the zwitterion **73** in an acidic medium (typically 45% aqueous acetic acid) is protonation and solvolytic cleavage of the three-membered ring. Evidently the rate of the reaction to form lumiketone is sensitive to the negative charge density on oxygen. Tautomerization gives the hydroxyketone (**77**).

A substituent at the β position of the dienone ring alters the symmetry of the molecule such that steric or electronic effects of the β substituent may direct the sigmatropic shift to one of two possible lumiketones (Eq 31). Certainly the most studied β substituent is that where R is the residue of a fused five- or six-membered ring. In almost all cases, ring strain directs the migration along path *b*. In systems unrestrained by ring fusions, β-substituents still may exhibit large directing effects. While their effects on hydroxyketone formation (i.e., during photolysis under acidic conditions) have not been investigated for monocyclic systems, their effects on regiochemistry of lumiketone formation have been studied. The simple dienone **80** (R = CH_3), upon photolysis in methanol, provides lumiketone **81**, the result of migration of bond *a*, the more substituted

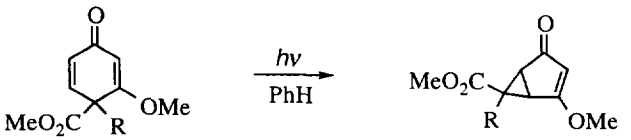
bond (Eq 32).[39] Similarly, photolysis of **80** (R = CCl_3) in *tert*-butanol provides only the lumiketones resulting from migration of bond *a* (**81**, as a 5:1 mixture of epimers).[40] Changing the β substituent to the strongly electron-withdrawing CN does not alter this selectivity pattern.[41,42] An electron-donating β-substituent, methoxy, has also been investigated in several examples. Cyclohexadienones such as **82** undergo conversion to lumiketones by migration of the more substituted bond, leaving the methoxy group on the newly-formed double bond (Eq 33),[43] while studies of other substrates have demonstrated low selectivity.[44] Generally, the β-effect seems relatively insensitive to the electron donating/withdrawing nature of the β substituent.



(31)



80 **81** (32)



82

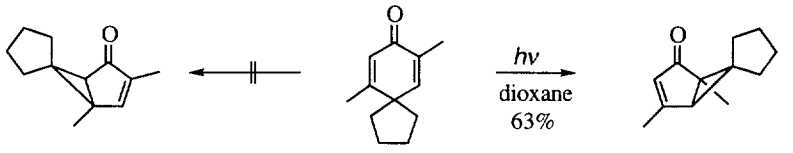
R = Me, Et, allyl

(33)

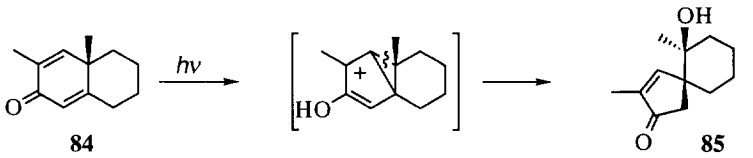
An α substituent, as with β substituents, changes the symmetry of a dienone and allows regiochemically distinguishable reactions of the zwitterion. Almost all studies of α-substituent effects have involved fused ring systems. Lumiketone formation is strongly affected by the geometric requirements of the ring fusion, so α-substituents are unlikely to change the bias in the [1,4] migration.[45,46] The behavior of one α-substituted dienone unconstrained by ring fusions has been reported. With **83**, [1,4] shift occurs such that the α–methyl group ends up on the three-membered ring rather than on the double bond (Eq 34).[47] However, the presence of the β-methyl group, which is known to direct the migration in this same sense, leaves unclear the role of the α substituent.

Regiochemical bias has been more carefully studied in the irradiation of α-substituted dienones under acidic conditions. Thus when **84** and **86** are irradiated in aqueous acid, regiospecific conversions to the spirodecane (**85**) and the fused 5/7 ring system (**87**), respectively, are observed (Eq 35).[47,48] Kropp has

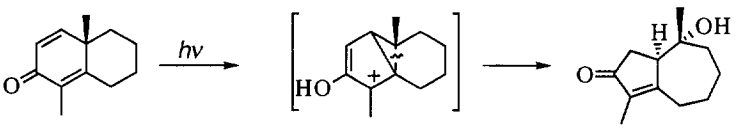
rationalized these results with the hypothesis that the α-methyl group, through inductive or hyperconjugative stabilization, localizes the positive charge at the site of substitution, facilitating cleavage of the bond proximal to the charge. Replacing the α-methyl group with an α-methoxy results in similar regioselectivity.[49] Related dienones lacking an α substituent experience no charge localization, and thus mixtures of spiro and fused-ring products are observed.[50] For dienones containing a simple 6/6 ring system, this model has strong predictive value, but with other ring systems, Kropp's model is less effective.



83 (34)

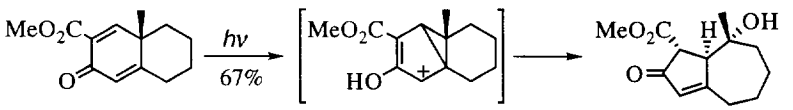


84 **85**

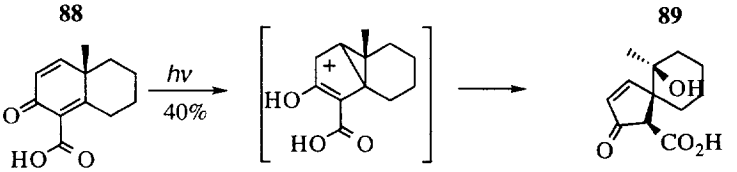


86 **87** (35)

This model for regioselectivity in hydroxyketone formation predicts that replacing an electron-donating α-substituent, such as methyl or methoxy, with an electron-withdrawing one should result in a reversal of selectivities, as observed with fused 6/6 dienones. Caine has shown that dienone **88** rearranges to the fused 5/7 rather than a spirocyclic system (Eq 36).[51] The same selectivity is observed with the α-carboxylic acid and the α-formyl compounds.[52,53]

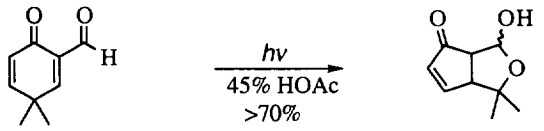


88 **89**



90 **91**
(as lactone) (36)

Conversely, dienone **90** rearranges to give the spirocyclic **91**.[54] Finally, there has been one report of the photoreactivity under acidic conditions of a monocyclic dienone bearing an α-substituent. Thus, **92** provides the intramolecular trapping product **93** (Eq 37), the same regiochemistry as observed in bicyclic systems.[54]



92 **93** (37)

The classical mechanistic pathway explains most of the results that we have observed with a special subset of cyclohexadienones, the quinone monoketals.

The results of (Eq 21, 22) should be compared to those of Feldman for the analogous dimethyl ketal **14** (Eq 7). Assuming **16** was also formed from the zwitterion (path *b*), Feldman also observed cleavage of the *more* substituted bond of the three-membered ring, though it is not at all clear why switching to the ethylene ketal and acetic acid solvent would reduce this selectivity so drastically.

This selectivity is contrary to the precedent in α-substituted 6/6 bicyclic dienones. In those systems, electron-donating α substituents (Me, OMe) direct the photolysis toward formation of the *more* substituted double bond. With electron-withdrawing α substituents, the less substituted double bond is formed (Eq 36, 37). Attempts to synthesize quinone ketals bearing electron-withdrawing groups were not successful, so the effects of substituent polarity could not be tested. It remains unclear how switching from 4,4-dialkyl to 4,4-dialkoxy substitution could effect this complete reversal of selectivity.

CONCLUSIONS

Quinone monoketals have proved useful substrates for the cyclohexadienone photorearrangement. By irradiation under acidic conditions they can be efficiently converted to cyclopentenones. Rules for predicting the stereochemistry and regiochemistry of the cyclopentenone products have been formulated through examination of reactants bearing all possible substitution patterns on the dienone ring. The reaction allows access to highly-substituted cyclopentenones, which should be of value in target-directed syntheses.

EXPERIMENTAL

General Procedure A: The Preparation of Hydroquinone Bisethers. The required hydroquinone was dissolved in DMF (~0.5 g/mL) in a flask equipped with a reflux condenser. A small portion (~20 mg) of NaH (60% in mineral oil) was added to the stirring solution. 2.2 mol-equivalents of ethylene carbonate were added, and the mixture was heated to 140 °C until CO_2 evolution had ceased (5-18 h). As was possible, solvent was removed by rotary evaporation. Most samples crystallized spontaneously and were purified by recrystallization from toluene/methanol. Some samples were induced to crystallize by dissolving in dichloromethane, washing with 10% aqueous NaOH, washing with brine, drying over Na_2SO_4, and rotary evaporation. Samples which could not be induced to crystallize were purified by flash chromatography using the indicated solvent system.

General Procedure B: The Electrochemical Oxidation of Hydroquinone Bisethers and the Monohydrolysis of Quinone Bisketals. The procedure is essentially that of Swenton.[15] A solution of the required bisether in 1-2% KOH/methanol (~1 g/25 mL) was cooled to 0 °C in a three neck flask. Bisethers showing poor solubility were run as a slurry. Using a woven, 2 cm x 4 cm, graphite cloth anode[55] and a 2 cm x 4 cm x 0.125 mm nickel foil cathode, the system was subjected to a constant current of ~0.5 A, with continuous stirring, until TLC showed loss of starting material. This current was readily available from a simple power supply, or an automotive battery charger regulated through a Variac. Solvent was then removed by rotary evaporation. The mixture was diluted with water and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over K_2CO_3;[56] and solvent was removed by rotary evaporation. Note that the leads to the electrodes (tinned copper) should be carefully cleaned or replaced between runs. The crude bisketal was dissolved (~1 g/25 mL) in THF/H_2O/HOAc (100:50:1). For ethylene ketals, the solution was heated to reflux until TLC indicated the loss of starting materials (7-20 h). For dimethyl ketals the solution was stirred at room temperature until TLC indicated the loss of starting materials (30-180 min). The bulk of the THF was removed by rotary evaporation. The reaction mixture was then neutralized with saturated $NaHCO_3$ or 5% NaOH and extracted with ether or CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over $MgSO_4$; and then solvents were removed by rotary evaporation. Flash chromatography on silica gel using the indicated solvent system provided pure products.

General Procedure C: The Photolysis of Quinone Monoketals. In a borosilicate glass tube equipped with a stir bar, dry nitrogen or argon was bubbled through glacial acetic acid for 15 min. The required quinone ketal was added to provide a concentration of 20-50 mM. Bubbling was continued for ~1 min until dissolution was complete. The tube was then capped with a septum cap, and irradiated, with stirring, through a uranium glass filter with a 450 W Hanovia lamp, model 679A3. Duration of irradiation varied with individual samples and lamps. Most reactions (~1 mmol scale) approached completion in 60-90 min, though irradiations as long as 12 h were sometimes required. The reaction can be followed by TLC (hexane/ethyl acetate—1:1). After most of the starting material was consumed, the solvent was removed by rotary evaporation. The residue was taken up in CH_2Cl_2 and neutralized with saturated aqueous $NaHCO_3$. The phases were separated, and the aqueous layer extracted twice more with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4; and then solvent was removed by rotary evaporation. Flash chromatography on silica gel using the indicated solvent system provided pure products.

7,9-Dimethyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one (20).[57] A solution of 3.0 g (22.0 mmol) 2,6-dimethylbenzoquinone, 45 mL ethylene glycol, 18 mL triethyl orthoformate, and 75 mg TsOH·H_2O in 135 mL CH_2Cl_2 was stirred for 10 d at room temperature, and triethylamine (2 mL) was added. The solution was poured into 150 mL saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with water (3x), with brine, and dried over $MgSO_4$. Following rotary evaporation, flash chromatography on silica (hexane/ether—9:1) provided 2.40 g (60%) of a pale yellow oil which crystallized on standing; mp 51-52 °C. IR (thin film): 2904, 1651, 1359, 1082, 958 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.40 (s, 2 H), 4.12 (s, 4 H), 1.88 (s, 6 H). UV (MeOH): 242 (3.21), 282 (2.74).

6,7,9-Trimethyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one (21). A solution of 3.31 g (22.0 mmol) trimethylbenzoquinone, 45 mL ethylene glycol, 18 mL triethyl orthoformate, and 75 mg TsOH·H_2O in 135 mL CH_2Cl_2 was stirred for 18 d at room temperature, and triethylamine (2 mL) was added. The solution was

poured into 150 mL saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic layers were washed with water (3x), with brine, and dried over $MgSO_4$. Following rotary evaporation, flash chromatography on silica (hexane/ether—4:1) provided 3.55 g (83%) of white crystals, mp 60.8-62.8 °C. IR (CCl_4): 2966, 2887, 1654, 1267, 1072, 948 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.46 (q, J = 1.4, 1H), 4.19 (s, 4H), 1.884 (s, 3H), 1.879 (s, 3H), 1.86 (d, J = 1.4, 3H). UV (MeOH): 246 (3.48), 290 (2.96); (Hexane): 224 (3.42), 282 (2.93), 354 (1.18). HRMS calcd for $C_{11}H_{14}O_3$: 194.0943. Found: 194.0942.

4,4-Dimethoxy-2,3-dimethyl-2,5-cyclohexadien-1-one (24). Using procedure B, 493 mg (3.0 mmol) 1,4-dimethoxy-2,3-dimethylbenzene[58] was converted to 311 mg (65%) of a pale yellow oil. ^1H NMR ($CDCl_3$): δ 6.70 (d, J = 10.5, 1H), 6.43 (d, J = 10.5, 1H), 3.19 (s, 6H), 1.91 (s, 6H). HRMS calcd for $C_{10}H_{14}O_3$: 182.0943. Found: 182.0937.

2,2'-(2-Methyl-1,4-phenylenedioxy)diethanol. Using procedure A, 4.60 g (37.1 mmol) of 2-methylhydroquinone was converted to 6.69 g (85%) of white crystals, mp 83.5-84.1 °C. IR (KBr): 3310, 2910, 1495, 1220, 1050 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.78-6.75 (m, 2H), 6.69 (dd, J = 8.7, 2.6, 1H), 4.05-4.02 (m, 4H), 3.99-3.91 (m, 4H), 2.23 (s, 3H). UV (MeOH): 234 (3.44), 289 (3.39). **Anal.** Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.01; H, 7.58.

4,4-Dimethoxy-3-(2-hydroxyethyl)-2,5-cyclohexadien-1-one (28). Using procedure B, 821 mg (4.51 mmol) 2-(2,5-dimethoxyphenyl)ethanol was converted to 582 mg (65%) of a pale yellow oil. IR (thin film): 3460, 2940, 1673, 1638, 1295, 1060 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.82 (d, J = 10.4, 1H), 6.41 (dd, J = 10.4, 2.6, 1H), 6.31 (m, 1H), 3.89 (dt, J = 5.6, 6.1, 2H), 3.28 (s, 6H), 2.58 (dt, J = 1.8, 6.1, 2H). HRMS calcd for $C_{10}H_{14}O_4$: 198.0892. Found: 198.0890. Evidence for the α substituted isomer was present in the ^1H NMR spectrum of the crude reaction mixture, but the compound was not isolated.

2,2'-(1,4-Phenylenedioxy)diethanol. Using procedure A, 2.76 g (25.1 mmol) hydroquinone was converted to 4.41 g (89%) of white crystals, mp 101.5-102.3 °C. IR (KBr): 3270, 2925, 1505, 1240, 1050 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.86 (s, 4H), 4.06-4.03 (m, 4H), 3.96-3.93 (m, 4H). UV (MeOH): 232 (3.50), 288 (3.47). **Anal.** Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.24; H, 7.11.

1,4-Dioxaspiro[4.5]deca-6,9-dien-8-one (29).[59] Using procedure B, 2.17 g (10.9 mmol) 2,2'-(1,4-phenylenedioxy)diethanol was converted to 1.42 g (85%) of pale yellow crystals, mp 50-51 °C, following chromatography (hexane/ether—1:2). ^1H NMR ($CDCl_3$): δ 6.63 (d, J = 10.2, 2H), 6.18 (d, J = 10.2, 2H), 4.16 (s, 4H). UV (MeOH): 237 (3.02), 261 (2.91).

7-Methyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one (30) and 6-Methyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one (31). Using procedure B, 4.58 g of 2,2'-(2-methyl-1,4-phenylenedioxy)diethanol was converted to two products upon chromatography (hexane/ether—1:2).

30: 836 mg (23%) of a pale yellow oil. IR (thin film): 2900, 1680, 1650, 1370, 1085, 975 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.61 (dd, J = 3.1, 10.1, 1H), 6.42 (dq, J = 3.1, 1.5, 1H), 6.17 (d, J = 10.1, 1H), 4.14 (s, 4H), 1.88 (d, J = 1.5, 3H). UV (MeOH): 234 (3.33), 287 (2.87). **Anal.** Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.09; H, 6.26.

31: 1.93 g (54%) of a pale yellow oil. IR (thin film): 2900, 1680, 1640, 1300, 1160, 975 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.66 (d, J = 10.0, 1H), 6.12 (dd, J = 10.0, 2.2, 1H), 6.07 (dq, J = 2.2, 1.4, 1H), 4.20 (s, 4H), 1.96 (d, J = 1.4, 3H). UV (MeOH): 235 (3.01), 280 (2.92). **Anal.** Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.80; H, 6.10.

2,2'-(2-*t*-Butyl-1,4-phenylenedioxy)diethanol. Using procedure A, 1.00 g (6.02 mmol) 2-*t*-butylhydroquinone was converted to 1.38 g (90%) of a reddish brown oil following chromatography (hexane/ethyl acetate—1:1). IR (thin film): 3363, 2920, 1475, 1218, 1067 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.93 (d, J = 3.1, 1H), 6.80 (d, J = 8.8, 1H), 6.70 (dd, J = 3.1, 8.8, 1H), 4.07-3.93 (m, 8H), 1.39 (s, 9H). UV (MeOH): 236 (3.20), 294 (3.21). HRMS calcd for $C_{14}H_{22}O_4$: 254.1518 Found: 254.1510.

7-*t*-Butyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one (32) and 6-*t*-Butyl-1,4-dioxa-spiro[4.5]deca-6,9-dien-8-one (33). Using procedure B, 1.54 g (6.05 mmol) 2,2'-(2-*tert*-butyl-1,4-phenylenedioxy)diethanol was converted to two products upon chromatography (hexane/ether—2:1).

32: 381 mg (30%) of a pale yellow oil. IR (thin film): 2970, 1675, 1640, 1370, 1150, 975 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.54 (dd, J = 3.1, 10.0, 1H), 6.36 (d, J = 3.1, 1H), 6.07 (d, J = 10.0, 1H), 4.17-4.13 (m, 4H), 1.22 (s, 9H). **Anal.** Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.85. Found: C, 68.63; H, 8.14.

33: 405 mg (32%) of a pale yellow oil. IR (thin film): 2980, 1670, 1640, 1300, 1130, 975 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.69 (d, J = 10.1, 1H), 6.30 (d, J = 2.1, 1H), 6.07 (dd, J = 2.1, 10.1, 1H), 4.28-4.20 (m, 4H), 1.27 (s, 9H). **Anal.** Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.85. Found: C, 69.37; H, 7.85.

2,2'-(2,3-Dimethyl-1,4-phenylenedioxy)diethanol. Using procedure A, 2.41 g (17.4 mmol) 2,3-dimethylhydroquinone was converted to 3.53 g (89%) of white crystals, mp 116.2-117.8 °C. IR (KBr): 3305, 2910, 1440, 1245, 1100 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.67 (s, 2H), 4.03-4.02 (m, 4H), 3.98-3.94 (m, 4H), 2.19 (s, 6H). UV (MeOH): 232 (3.47), 286 (3.37). **Anal.** Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.58; H, 8.11.

6,7-Dimethyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one (34). Using procedure B, 2.00 g (8.84 mmol) 2,2'-(2,3-dimethyl-1,4-phenylenedioxy)diethanol was converted to 1.39 g (87%) of white crystals, mp 86.4-87.9 °C following chromatography (hexane/ether—1:1). IR (CCl_4): 2900, 1680, 1650, 1310, 1065, 960 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.66 (d, J = 10.0, 1H), 6.14 (d, J = 10.0, 1H), 4.23-4.20 (m, 4H), 1.91 (d, J = 1.0, 3H), 1.88 (d, J = 1.0, 3H). UV (MeOH): 237 (3.17), 289 (3.09). **Anal.** Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.74; H, 6.74.

2,2'-(2,5-Dimethyl-1,4-phenylenedioxy)diethanol. Using procedure A, 1.71 g (12.4 mmol) 2,5-dimethylhydroquinone was converted to 1.75 g (63%) of white crystals, mp 142.3-144.1 °C. IR (nujol): 3252, 1512, 1213, 1084 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.59 (s, 2H), 4.04-4.01 (m, 2H), 3.95-3.91 (m, 4H), 3.86-3.84 (m, 2H), 2.27 (s, 6H). UV (MeOH): 218 (3.38), 288 (3.30). HRMS Calcd. for $C_{12}H_{18}O_4$: 226.1205. Found: 226.1204.

6,9-Dimethyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one (35). Using procedure B, 1.28 g (5.66 mmol) 2,2'-(2,5-dimethyl-1,4-phenylenedioxy)diethanol was converted to 699 mg (69%) of pale yellow crystals, mp 35.0-36.4 °C following chromatography (hexane/ether—65:35). IR (thin film): 2900, 1685, 1645, 1370, 1075, 970 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.45 (q, J = 1.5, 1H), 6.05 (q, J = 1.5, 1H), 4.20-4.16 (m, 4H), 1.94 (d, J = 1.5, 3H), 1.86 (d, J = 1.5, 3H). UV (MeOH): 246 (3.28), 280 (2.98). HRMS calcd for $C_{10}H_{12}O_3$: 180.0786. Found: 180.0777.

2,2'-(2,5-Di-*tert*-butyl-1,4-phenylenedioxy)diethanol. Using procedure A, 5.00 g (22.5 mmol) 2,5-di-*t*-butylhydroquinone was converted to 5.40 g (77%) of white crystals, mp 135.5-137.1 °C. IR (KBr): 3260, 2950, 1505, 1375, 1205, 1055 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.85 (s, 2H), 4.12-4.10 (m, 4H), 4.02-3.98 (m,

4H), 1.38 (s, 18H). UV (MeOH): 237 (3.35), 292 (3.34). **Anal.** Calcd. for $C_{12}H_{18}O_4$: C, 69.64; H, 9.74. Found: C, 69.68; H, 9.83.

6,9-Di-*tert*-Butyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one (36). Using procedure B, 1.07 g (3.44 mmol) 2,2'-(2,5-di-*tert*-butyl-1,4-phenylenedioxy)diethanol was converted to 603 mg (66%) of white crystals, mp 105.5-106.7 °C, following chromatography (hexane/ether—8:1). IR (CCl_4): 2970, 1670, 1640, 1380, 1130, 970 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.37 (s, 1H), 6.18 (s, 1H), 4.23 (m, 4H), 1.25 (s, 9H), 1.21 (s, 9H). UV (MeOH): 246 (3.50), 284 (3.01). **Anal.** Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.75; H, 9.31.

2,2'-(2,6-Dimethyl-1,4-phenylenedioxy)diethanol. Using procedure A, 771 mg (5.58 mmol) of 2,6-dimethylhydroquinone was converted to 923 mg (73%) of white crystals, mp 91.6-92.4 °C, following chromatographic workup (hexane/ethyl acetate—6:4). IR (KBr): 3320, 2935, 1475, 1220, 1060 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.59 (s, 2H), 4.04-4.01 (m, 2H), 3.95-3.91 (m, 4H), 3.86-3.84 (m, 2H), 2.27 (s, 6H). UV (MeOH): 210 (3.70), 281 (3.34). HRMS calcd for $C_{12}H_{18}O_4$: 226.1205. Found: 226.1202.

6,10-Dimethyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one (37). Using procedure B, 661 g (2.92 mmol) of 2,2'-(2,6-dimethyl-1,4-phenylenedioxy)diethanol was converted to 296 mg (56%) of white crystals, mp 76.3-78.0 °C following chromatography (hexane/ether—4:6). IR (CCl_4): 2895, 1675, 1648, 1300, 1032, 970 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.97 (s, 2H), 4.31 (s, 4H), 1.96 (d, J = 1.6, 6H). UV (MeOH): 239 (3.53), 277 (3.19). HRMS calcd for $C_{10}H_{12}O_3$: 180.0786. Found: 180.0786.

2,2'-(2,3,5-Trimethyl-1,4-phenylenedioxy)diethanol. Using procedure A, 5.20 g (34.1 mmol) 2,3,5-trimethylhydroquinone was converted to 6.58 g (80%) of white crystals, mp 99.1-99.8 °C. IR (KBr): 3340, 2910, 1450, 1225, 1070 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.57 (s, 1H), 4.05-4.02 (m, 2H), 3.98-3.92 (m, 4H), 3.81-3.83 (m, 2H), 2.28 (s, 3H), 2.22 (s, 3H), 2.15 (s, 3H). UV (MeOH): 231 (3.25), 282 (3.21). A sample for analysis was subsequently recrystallized from toluene/methanol. **Anal.** Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.72; H, 8.41.

6,7,10-Trimethyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one (38). Using procedure B, 4.09 g (17.0 mmol) 2,2'-(2,3,5-trimethyl-1,4-phenylenedioxy)diethanol was converted to 2.75 g (83%) of pale yellow crystals, mp 36.4-37.5 °C, following chromatography (hexane/ether—1:1). IR (thin film): 2900, 1680, 1640, 1180, 1080, 960 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.98 (q, J = 1.5, 1H), 4.35-4.31 (m, 4H), 1.94 (d, J = 1.4, 3H), 1.89 (d, J = 0.9, 3H), 1.84 (d, J = 0.9, 3H). UV (MeOH): 238 (3.35), 290 (3.15). **Anal.** Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.83; H, 7.26.

2,2'-(2,3,5,6-Tetramethyl-1,4-phenylenedioxy)diethanol. Using procedure A, 764 mg (4.65 mmol) tetramethylhydroquinone was converted to 808 mg (68%) of white crystals, mp 162.7-163.3 °C, following chromatography (hexane/ethyl acetate—7:3) and recrystallization from toluene/methanol. IR (KBr): 3470, 2940, 1455, 1260, 1075 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.98-3.94 (m, 4H), 3.81-3.79 (m, 4H), 2.18 (s, 12H). UV (MeOH): 216 (3.52), 275 (2.74). A sample for analysis was subsequently recrystallized from toluene/methanol. **Anal.** Calcd. for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.81; H, 8.80.

6,7,9,10-Tetramethyl-1,4-dioxaspiro[4.5]deca-6,9-dien-8-one (39). Using procedure B, 507 mg (1.99 mmol) of 2,2'-(2,3,5,6-tetramethyl-1,4-phenylenedioxy)diethanol was subjected to oxidation and hydrolysis. Recrystallization from hexanes/ethyl acetate of the crude reaction product provided 42 mg (8%) of recovered starting material. Flash chromatography of the mother liquor (hexane/ether—7:3) gave 150 mg (39% based on recovered SM) of white needles, mp 119.0-119.6 °C. IR (CCl_4): 2900, 1645, 1210, 1090, 955

cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.35 (s, 4H), 1.89 (d, J = 0.9, 6H), 1.86 (d, J = 0.9, 6H). UV (MeOH): 238 (3.58), 296 (3.06). **Anal.** Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.26; H, 8.05.

3,3,7-Trimethyl-1,5-dioxaspiro[5.5]undeca-7,10-dien-9-one (46). To tolquinone dimethyl ketal **23** (201 mg, 1.2 mmol) was added by syringe dimethylpropanediol (4-5 mol equivalents) and DME (20 mL). A slight excess (1.05 mol-equivalents, relative to ketal) of a 1-2 M solution of $BF_3 \cdot Et_2O$ in DME was added dropwise at ambient temperature with rapid stirring over 2 min. The solution was stirred an additional 3 min, by which time TLC indicated complete conversion. The reaction mixture was quenched with an equal volume of 10% NaOAc. The solution was extracted with ether (3x), and the combined organic layers were washed with brine and dried over Na_2SO_4. Following rotary evaporation, the title compound (180 mg, 72%) was obtained by flash chromatography on silica gel (hexane/ether—3:1) as colorless needles, mp 82.8-84.6 °C, IR (CCl_4): 2960, 2870, 1682, 1650, 1198, 1109, 982 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.62 (d, J = 10.6, 1H), 6.21 (dd, J = 2.0, 10.6, 1H), 6.05 (dq, J = 2.0, 1.4, 1H), 3.93 (d, J = 11.8, 2H), 3.54 (d, J = 11.8, 2H), 2.15 (d, J = 1.4, 3H), 1.33 (s, 3H), 0.85 (s, 3H). UV (Hexane): 222 (3.58), 260 (3.29), 360, (0.59). **Anal.** Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.35; H, 7.92. Traces (~3%) of the α-methyl isomer (identified by ^1H NMR and TLC characteristics) were also observed. These were readily separated during chromatography. IR (CCl_4): 2959, 2868, 1682, 1655, 1198, 1085, 985 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.16 (dd, J = 10.3, 3.2, 1H), 6.89-6.84 (m, 1H), 6.20 (d, J = 10.3, 1H), 3.71 (d, J = 11.2, 2H), 3.68 (d, J = 11.2, 2H), 1.90 (d, J = 1.4, 3H), 1.10 (s, 3H), 1.04 (s, 3H).

1,5-Dioxaspiro[5.5]undeca-7,10-dien-9-one (44).[60] Using the above procedure, 257 mg (1.67 mmol) of **9** was converted to 203 mg (73%) of colorless needles, mp 72.4-73.9 °C, following chromatography (hexane/ether—6:4). IR (CCl_4): 2969, 2875, 1688, 1642, 1388, 1183, 996 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.15 (d, J = 10.4, 2H), 6.20 (d, J = 10.4, 2H), 4.10 (t, J = 5.6, 4H), 1.91 (quintet, J = 5.6, 2H). UV (Hexane): 224 (3.60), 260 (3.00), 366 (1.10).

3,3-Dimethyl-1,5-dioxaspiro[5.5]undeca-7,10-dien-9-one (45). Using the above procedure, 108 mg (0.70 mmol) **9** was converted to 97 mg (77%) of colorless needles, mp 68.3-70.6 °C, following chromatography (hexane/ether—8:2). IR (CCl_4): 2959, 2869, 1690, 1644, 1393, 1188, 996 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.14 (d, J = 10.3, 2H), 6.20 (d, J = 10.3, 2H), 3.70 (s, 4H), 1.07 (s, 6H). UV (Hexane): 222 (3.43), 256 (3.04), 362, (1.05). HRMS calcd for $C_{11}H_{15}O_3$ [MH^+]: 195.1021. Found: 195.1021.

2-(Trimethoxymethyl)-2-cyclopenten-1-one (48). Monoketal **9** (147 mg, 0.953 mmol) was dissolved in 19.1 mL methanol in a base-washed Pyrex tube. A drop of triethylamine was added, and dry nitrogen was bubbled through the solution for 15 min. The tube was capped and wired to the side of a vacuum jacketed, 450 W Hanovia medium pressure lamp equipped with a uranium glass filter. The lamp and reaction vessel were then immersed in a dry ice/isopropanol bath and the sample was irradiated for 18 h. Solvent was removed by rotary evaporation, and the resulting brown oil was dissolved in water and extracted (3x) with CH_2Cl_2. The combined organic layers were washed with brine and dried with Na_2SO_4. The solvent was removed by rotary evaporation. Flash chromatography on silica (hexane/ethyl acetate—1:1) provided 133 mg (75%) of pale yellow crystals, mp 40.0-41.0 °C. IR (thin film): 2950, 1708, 1440, 1325, 1107 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.91 (t, J = 2.7, 1H), 3.19 (s, 9H), 2.69-2.66 (m, 2H), 2.53-2.50 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 204.6, 166.2, 141.0, 112.2, 49.7, 35.7, 26.0. UV (MeOH): 212 (3.24), 235 (3.24), 300 (2.04). HRMS calcd for $C_9H_{14}O_4$: 186.0892. Found: 186.0898.

2-Hydroxyethyl 4-Oxo-2-cyclopentenecarboxylate (49). Using procedure C, 107 mg of **29** was converted to 97.9 mg (82%) of a pale yellow oil following chromatography (hexanes/ethyl acetate—2:8). IR (thin film): 3410, 2960, 1705, 1675, 1190, 1080 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.71 (dd, J = 5.6, 2.8, 1H), 6.29 (dd, J = 5.6, 2.4, 1H), 4.32-4.25 (m, 2H), 3.97-3.94 (m, 1H), 3.89-3.83 (m, 2H), 2.79 (dd, J = 18.9, 2.8, 1H), 2.64 (dd, J = 18.9, 7.1, 1H). HRMS Calcd. for $C_9H_{14}O_4$: 186.0892. Found: 186.0895.

2-Hydroxyethyl 1,2-Dimethyl-4-oxo-2-cyclopentenecarboxylate (50). Using procedure C, 105 mg of **37** was converted to 92.0 mg (79%) of a pale yellow oil following chromatography (hexanes/ethyl acetate—3:7). IR (thin film): 3450, 2970, 1725, 1690, 1620, 1265, 1180 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.99 (q, J = 1.2, 1H), 4.27-4.24 (m, 2H), 3.84-3.80 (m, 2H), 2.96 (d, J = 18.4, 1H), 2.31 (d, J = 18.4, 1H), 2.09 (d, J = 1.2, 3H), 1.50 (s, 3H); HRMS calcd for $C_{10}H_{15}O_4$ [MH^+]: 199.0970. Found: 199.0964.

2-Hydroxyethyl 3,5-Dimethyl-4-oxo-2-cyclopentenecarboxylate (51). Using procedure C, 101 mg of **20** was converted to 71.7 mg (64%) of a pale yellow oil following chromatography (hexane/ethyl acetate—1:1). ^1H NMR spectroscopy indicates an 11:1 mixture of epimers. An additional 18 mg (18%) of starting material was also recovered (78% yield based on recovered starting material). IR (thin film): 3432, 2936, 1717, 1332, 1215, 1081 cm^{-1}. ^1H NMR ($CDCl_3$) (Major diastereomer): δ 7.23 (m, 1H), 4.32-4.26 (m, 2H), 3.91-3.85 (m, 2H), 3.35 (m, 1H), 2.70 (dq, J = 3.2, 7.4, 1H), 1.82 (m, 3H), 1.29 (d, J = 7.4, 3H). HRMS calcd for $C_{10}H_{14}O_4$: 198.0892. Found: 198.0890.

2-Hydroxyethyl 1,2,3,5-Tetramethyl-4-oxo-2-cyclopentenecarboxylate (52). Using procedure C, 45.4 mg of **39** was converted to 40.0 mg (81%) of a pale yellow oil following chromatography (hexanes/ethyl acetate—1:1). ^1H NMR spectroscopy indicates a 1.3:1 mixture of epimers. IR (thin film): 3450, 2990, 1730, 1705, 1650, 1455, 1245, 1080 cm^{-1}. ^1H NMR ($CDCl_3$) Major epimer: δ 4.29-4.23 (m, 2H), 3.85-3.81 (m, 2H), 2.77 (q, J = 7.5, 1H), 2.00 (s, 3H), 1.73 (s, 3H), 1.59 (s, 3H), 1.14 (d, J = 7.5, 3H); Minor epimer: δ 4.22-4.18 (m, 2H), 3.80-3.76 (m, 2H), 2.25 (q, J = 7.5, 1H), 1.97 (s, 3H), 1.75 (s, 3H), 1.28 (s, 3H), 1.12 (d, J = 7.5, 3H). UV (MeOH): 242 (3.30). HRMS Calcd. for $C_{12}H_{18}O_4$: 226.1205. Found: 226.1207.

2-Hydroxyethyl 1-Methyl-4-oxo-2-cyclopentenecarboxylate (54) and 2-Hydroxyethyl 2-Methyl-4-oxo-2-cyclo-pentenecarboxylate (53). Using procedure C, 144 mg of **31** was converted to two products, separable on chromatography (hexanes/ethyl acetate—2:8).

54: 36.7 mg (23%) of a pale yellow oil. IR (thin film): 3425, 2970, 1705, 1590, 1450, 1275, 1170 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.62 (d, J = 5.6, 1H), 6.17 (d, J = 5.6, 1H), 4.27-4.23 (m, 2H), 3.87-3.83 (m, 2H), 3.01 (d, J = 18.5, 1H), 2.28 (d, J = 18.5, 1H), 1.54 (s, 3H). HRMS Calcd. for $C_9H_{12}O_4$: 184.0736. Found: 184.0728.

53: 70.2 mg (44%) of a pale yellow oil. IR (thin film): 3410, 2950, 1720, 1670, 1615, 1430, 1325, 1180 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.06-6.04 (m, 1H), 4.37-4.24 (m, 2H), 3.95-3.81 (m, 2H), 3.75-3.70 (m, 1H), 2.74 (dd, J = 18.4, 3.1, 1H), 2.66 (dd, J = 18.4, 7.1, 1H), 2.19 (s, 3H). HRMS Calcd. for $C_9H_{12}O_4$: 184.0736. Found: 184.0744.

2-Hydroxyethyl 1,3,5-Trimethyl-4-oxo-2-cyclopentenecarboxylate (56) and 2-Hydroxyethyl 2,3,5-Trimethyl-4-oxo-2-cyclopentenecarboxylate (55). Using procedure C, 135.3 mg of **21** was converted to two compounds in a 1:1.1 ratio. The two compounds were partially resolved by chromatography (hexanes/ether—4:6).

56: 31.5 mg (26%) of a colorless oil. ^{1}H NMR spectroscopy indicates a 2.6:1 mixture of epimers. IR (thin film): 3445, 2945, 1715, 1642, 1453, 1235, 1081 cm^{-1}. ^{1}H NMR ($CDCl_3$) Major epimer: δ 7.25 (q, J = 1.3, 1H), 4.29-4.25 (m, 2H), 3.88-3.83 (m, 2H), 2.82 (q, J = 7.4, 1H), 1.80 (d, J = 1.4, 3H), 1.31 (s, 3H), 1.19 (d, J = 7.4, 3H); Minor epimer: δ 7.10 (d, J = 1.4, 1H), 4.23-4.19 (m, 2H), 3.83-3.78 (m, 2H), 2.27 (q, J = 7.4, 1H), 1.83 (d, J = 1.4, 3H), 1.48 (s, 3H), 1.13 (d, J = 7.4, 3H). HRMS calcd for $C_{11}H_{16}O_4$: 212.1048. Found: 212.1045.

55: 13.1 mg (9%) of a colorless oil. By ^{1}H NMR spectroscopy, only one epimer of this compound could be identified. IR (thin film): 3431, 2937, 1731, 1696, 1649, 1332, 1176, 1083 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 4.37-4.24 (m, 2H), 3.90-3.85 (m, 2H), 3.24-3.23 (m, 1H), 2.63 (dq, J = 3.0, 7.5, 1H), 2.06 (s, 3H), 1.74 (d, J = 0.9, 3H), 1.25 (d, J = 7.4, 3H). HRMS calcd for $C_{11}H_{16}O_4$: 212.1048. Found: 212.1049.

An additional 64.9 mg (44%) of a mixture of **55** and **56** was isolated, as well as 25.0 mg (18%) of starting material (91% combined yield based on recovered starting material).

2-Hydroxyethyl 5-Methyl-4-oxo-2-cyclopentenecarboxylate (57). Using procedure C, 97 mg of **30** was converted to 85.0 mg (79%) of a pale yellow oil following chromatography (hexanes/ethyl acetate—2:8). ^{1}H NMR spectroscopy indicates a 10:1 mixture of epimers. ^{1}H NMR ($CDCl_3$) Major diastereomer: δ 7.64 (dd, J = 5.8, 2.5, 1H), 6.27 (dd, J = 5.8, 2.4, 1H), 4.36-4.29 (m, 2H), 3.90-3.87 (m, 2H), 3.49 (m, 1H), 2.70 (dq, J = 7.5, 3.4, 1H), 1.30 (d, J = 7.5, 1H). HRMS Calcd. for $C_9H_{12}O_4$: 184.0736. Found: 184.0732.

2-Hydroxyethyl 1,2,5-Trimethyl-4-oxo-2-cyclopentenecarboxylate (58). Using procedure C, 48.5 mg of **38** was converted to 44.6 mg (84%) of a pale yellow oil following chromatography (hexanes/ether—1:1). ^{1}H NMR spectroscopy indicates a 1.5:1 mixture of epimers. IR (thin film): 3440, 2990, 1725, 1705, 1625, 1450, 1240, 1090 cm^{-1}. ^{1}H NMR ($CDCl_3$) Major epimer: δ 5.98 (d, J = 1.3, 1H), 4.30-4.25 (m, 2H), 3.86-3.82 (m, 2H), 2.84 (q, J = 7.5, 1H), 2.11 (d, J = 1.3, 3H), 1.33 (s, 3H), 1.14 (d, J = 7.5, 3H); Minor epimer: δ 6.05 (d, J = 1.4, 1H), 4.24-4.20 (m, 2H), 3.82-3.79 (m, 2H), 2.32 (q, J = 7.5, 1H), 2.07 (d, J = 1.1, 3H), 1.49 (s, 3H), 1.12 (d, J = 7.5, 3H). ^{13}C NMR ($CDCl_3$) Major epimer: δ 208.88, 177.80, 174.05, 129.47, 66.69, 60.76, 58.06, 49.93, 18.13, 15.70, 10.27; Minor epimer: δ 208.24, 176.30, 172.46, 130.83, 66.62, 60.62, 56.48, 53.03, 20.92, 15.64, 10.54. UV (MeOH): 237 (3.07), 286 (2.24). HRMS Calcd. for $C_{11}H_{16}O_4$: 212.1048. Found: 212.1048.

2-Hydroxyethyl 2,5-Dimethyl-4-oxo-2-cyclopentenecarboxylate (59). Using procedure C, 103.1 mg of **35** was converted to 54.5 mg (48%) of a colorless oil following chromatography (hexanes/ethyl acetate—1:1). ^{1}H NMR spectroscopy indicates a 7:1 mixture of epimers. IR (thin film): 3430, 2980, 1735, 1700, 1625, 1185, 1090 cm^{-1}. ^{1}H NMR ($CDCl_3$) Major epimer: δ 6.03-6.01 (m, 1H), 4.33-4.28 (m, 2H), 3.90-3.86 (m, 2H), 3.31-3.32 (m, 1H), 2.71 (dq, J = 7.5, 3.1, 1H), 2.17 (s, 3H), 1.26 (d, J = 7.5, 3H). UV (MeOH): 212 (3.36), 240 (3.35), 307 (1.72). HRMS Calcd. for $C_{10}H_{14}O_4$: 198.0892. Found: 198.0897.

2-Hydroxyethyl 1,5-Dimethyl-4-oxo-2-cyclopentenecarboxylate (61). Using procedure C, 58.3 mg of **34** was converted to 57.1 mg (89%) of a pale yellow oil following chromatography (hexanes/ethyl acetate—3:7). ^{1}H NMR spectroscopy indicated a 2:1 mixture of epimers. IR (thin film): 3440, 2990, 1710, 1595, 1455, 1245, 1130 cm^{-1}. ^{1}H NMR ($CDCl_3$) Major diastereomer: δ 7.66 (d, J = 5.8, 1H), 6.18 (d, J = 5.8, 1H), 4.30-4.24 (m, 2H), 3.87-3.85 (m, 2H), 2.80 (q, J = 7.5, 1H), 1.35 (s, 3H), 1.21 (d, J = 7.5, 3H); Minor diastereomer: δ 7.50 (d, J = 5.8, 1H), 6.26 (d, J = 5.8, 1H), 4.23-4.21 (m, 2H), 3.82-3.80 (m, 2H), 2.27 (q, J =

7.2, 1H), 1.52 (s, 3H), 1.14 (d, J = 7.2, 3H). UV (MeOH): 237 (3.13). HRMS calcd for $C_{10}H_{14}O_4$: 198.0892. Found: 198.0894.

2-Hydroxyethyl 1,3-Di-*tert*-butyl-4-oxo-2-cyclopentenecarboxylate (62). Using procedure C, 111 mg of **36** was converted to 33.0 mg (28%) of a colorless oil following chromatography (hexanes/ethyl acetate—7:3). IR (thin film): 3440, 2970, 1735, 1700, 1470, 1260, 1175 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.31 (s, 1H), 4.31-4.23 (m, 2H), 3.88-3.84 (m, 2H), 2.81 (d, J = 19.1, 1H), 2.59 (d, J = 19.1, 1H), 1.20 (s, 9H), 0.99 (s, 9H). HRMS calcd for $C_{16}H_{24}O_3$ [M - H_2O]: 264.1725. Found: 264.1722.

2-Hydroxyethyl 5-*tert*-Butyl-4-oxo-2-cyclopentenecarboxylate (63). Using procedure C, 115.1 mg of **32** was converted to 53.1 mg (42%) of a pale yellow oil following chromatography (hexanes/ethyl acetate—6:4). ^1H NMR ($CDCl_3$) Major epimer: δ 7.58 (dd, J = 2.8, 5.7, 1H), 6.19 (dd, J = 2.3, 5.7, 1H), 4.33-4.25 (m, 2H), 3.89-3.86 (m, 2H), 3.72-3.70 (m, 1H), 2.58 (d, J = 2.8, 1H), 1.02 (s, 9H). HRMS Calcd. for $C_{12}H_{18}O_4$: 226.1205. Found: 226.1209.

3-Hydroxypropyl 4-Oxo-2-cyclopentenecarboxylate (64). Using procedure C, 91.2 mg of **44** was converted to 41.3 mg (41%) of a pale yellow oil following chromatography (hexanes/ethyl acetate—2:8). ^1H NMR ($CDCl_3$): δ 7.68 (dd, J = 5.6, 2.7, 1H), 6.27 (dd, J = 5.6, 2.3, 1H), 4.32 (t, J = 6.3, 2H), 3.93-3.88 (m, 1H), 3.72 (t, J = 6.0, 2H), 2.76 (dd, J = 18.9, 2.9, 1H), 2.60 (dd, J = 18.9, 7.1, 1H), 1.92 (tt, J = 6.0, 6.3, 2H). Minor isomer **65** (partial spectrum): δ 7.09 (quintet, J = 2, 1H), 4.45 (t, J = 5.7, 2H), 3.84 (t, J = 5.5, 2H), 3.16 (d, J = 2.0, 2H), 3.13 (d, J = 2.5, 2H). HRMS Calcd. for $C_9H_{12}O_4$: 184.0736. Found: 184.0730.

2,2-Dimethyl-3-hydroxypropyl 4-Oxo-2-cyclopentenecarboxylate (66). Using procedure C, 104.6 mg of **45** was converted to 39.6 mg (35%) of a pale yellow oil following chromatography (hexanes/ethyl acetate—2:8). ^1H NMR ($CDCl_3$): δ 7.67 (dd, J = 5.6, 2.8, 1H), 6.28 (dd, J = 5.6, 2.4, 1H), 4.02 (s, 2H), 3.94-3.90 (m, 1H), 3.33 (d, J = 5.6, 2H), 2.76 (dd, J = 18.9, 2.8, 1H), 2.61 (dd, J = 18.9, 7.1, 1H), 0.94 (s, 6H). Minor isomer **67** (partial spectrum): δ 7.11 (quintet, J = 2, 1H), 4.06 (s, 2H), 3.18 (d, J = 2, 2H), 3.14 (d, J = 2, 2H). HRMS Calcd. for $C_{11}H_{16}O_4$: 212.1048. Found: 212.1039.

2,2-Dimethyl-3-hydroxypropyl 1-Methyl-4-oxo-2-cyclopentenecarboxylate (69) and 2,2–Dimethyl–3–hydroxypropyl 2–Methyl–5–oxo–1–cyclopentene–carboxylate (68). Using procedure C, 105.4 mg of **151** was converted to two products on chromatography (hexanes/ethyl acetate—6:4).

69: 28.4 mg (25%) of a colorless oil. IR (thin film): 3453, 2939, 1720, 1273, 1181, 1055 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.59 (d, J = 5.6, 1H), 6.17 (d, J = 5.6, 1H), 4.00 (d, J = 10.9, 1H), 3.97 (d, J = 10.9, 1H), 3.30 (d, J = 3.1, 2H), 2.99 (d, J = 18.7, 1H), 2.27 (d, 18.7, 1H), 1.54 (s, 3H), 0.92 (s, 6H). HRMS Calcd. for $C_{11}H_{16}O_4$: 212.1048. Found: 212.1052.

68: 64.2 mg (56%) of a colorless oil. IR (thin film): 3473, 2932, 1720, 1631, 1229, 1045 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.06 (s, 2H), 3.46 (s, 2H), 2.72-2.68 (m, 2H), 2.52-2.48 (m, 2H), 2.46 (s, 3H), 0.98 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 204.0, 187.6, 163.1, 131.7, 72.1, 69.9, 35.9, 34.9, 32.9, 21.8, 19.5. HRMS Calcd. for $C_{11}H_{16}O_4$: 212.1048. Found: 212.1038.

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