

**Photochemistry of Alkylated 4,4-Dimethoxy-2,5-cyclohexadienones in Methanol.
Synthesis of Methyl Ester of (\pm)-Desepoxy-2,5-didehydromethylenomycin A¹**

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Abstract: Alkylated 4,4-dimethoxy-2,5-cyclohexadienones were irradiated in methanol to give 2-cyclopentenones derivatives in fair yields. Methyl ester of (\pm)-desepoxy-2,5-didehydromethylenomycin A was prepared from 2,3-dimethylhydroquinone monomethyl ether in four steps and 36% overall yield using this photochemical reaction as a key step.

The photorearrangements of 2,5-cyclohexadienones have been extensively investigated;² the photochemistry of masked *p*-benzoquinones, which are 2,5-cyclohexadienones possessing dialkoxy groups at the C(4) position, are less well known.³ Pirrung et al.^{3c} reported that irradiation of ethylene monoketals of various alkyl-substituted *p*-benzoquinones in acetic acid afforded 4-methoxycarbonyl-2-cyclopentenones in high yields. We have examined the irradiation of alkylated 4,4-dimethoxy-2,5-cyclohexadienones in methanol, through a uranium-glass filter. 2-Cyclopentenone derivatives were produced in fair to excellent yields depending on the positions of the alkyl substituents. The regiochemistry of the photochemical reactions of masked *p*-benzoquinones in our reaction conditions differs from that in acetic acid studied by Pirrung et al.^{3c} We report herein our findings and also the results of using this photochemical reaction as a key step in the synthesis of methyl ester of (\pm)-desepoxy-2,5-didehydromethylenomycin A.⁴

Masked *p*-benzoquinones 1-6 were prepared from the oxidation of the monomethyl ether of the corresponding hydroquinones by thallium(III) nitrate (TTN)⁵ in anhydrous methanol in the presence of excess potassium carbonate. The irradiation was carried out in the following manner. A solution of masked *p*-benzoquinone in methanol (0.01-0.02 M) was placed in a Pyrex tube, bubbled with nitrogen for 45 min, properly stoppered and irradiated in a Rayonet reactor with light of wavelength 350 nm through a uranium-glass filter until the complete disappearance of masked *p*-benzoquinone as indicated by TLC and GC analyses. The irradiated mixtures are generally quite complicated. The major products were isolated by preparative-layer or column chromatography. The results are summarized in Table 1. The structures of the products were determined from their spectral data or by comparison with those of known compounds (10⁶, 12⁷). The ethyl ester of compound 12 has been reported to be as an intermediate in the synthesis of methylenomycin B.⁷

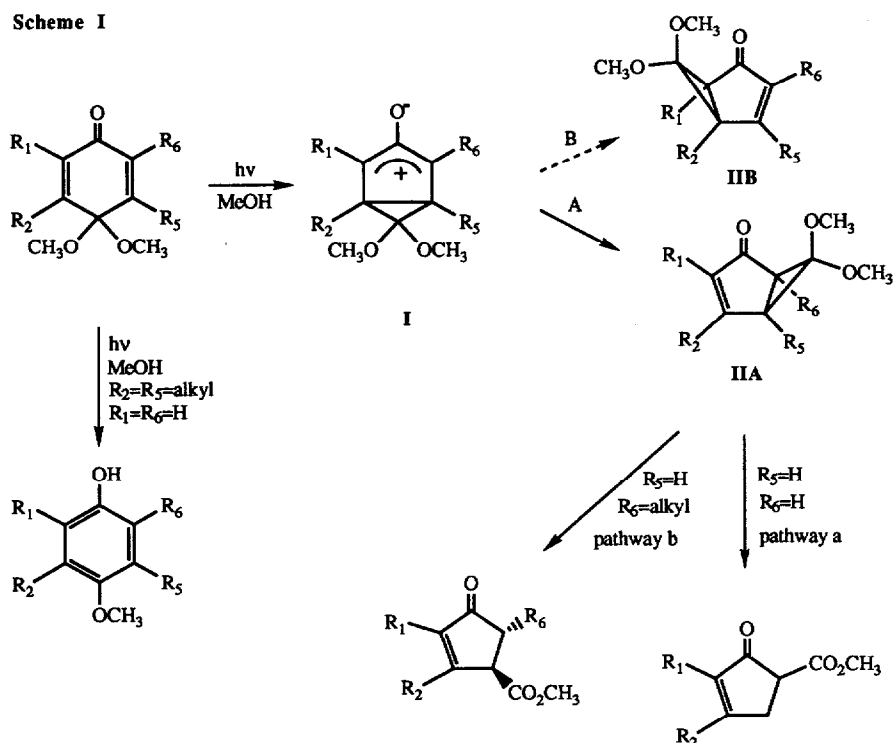
The mechanism of the formation of 2-cyclopentenones from irradiated masked *p*-benzoquinones presumably involves the intermediacy of I.² There are, in principle, two possible routes (A or B) for the formation of bicyclo[3.1.0]hex-3-en-2-one intermediates (II) in the cases of 1-3, and 6; however only route A occurred. The more substituted alkene moieties of masked *p*-benzoquinones remained as alkene moieties in the cyclopentenone photoproducts. Furthermore, there are also two possible pathways (a or b) for the opening of

the dimethoxycyclopropane rings of the intermediates **IIA**. When there was no substituent ($R_6=H$) at the C(5) position of **IIA**, cleavage of the C(4)-C(6) bond (pathway a) took place to give 5-methoxycarbonylcyclopentenones as shown in entries 1-3 and 6 in Table 1; in contrast, when there was an alkyl substituent at the C(5) position of **IIA**, rupture of the C(5)-C(6) bond (pathway b) to generate 4-methoxycarbonylcyclopentenone occurred as shown in the entry 4. For entry 5, phenolic compound **11** was isolated as the major characterizable product; the reason is presumably that the steric repulsions between the substituents prevent the formation of intermediate **I**. Homolytic cleavage of the C(4)-OCH₃ bond followed by hydrogen abstraction reaction yielded **11**.⁸

Table 1. The Result of Preparation and Photochemical Reaction of Masked *p*-benzoquinones 1-6

Entry	Hydroquinone monomethyl ether	Masked <i>p</i> -Benzoquinone (Yield)	Photoproduct (Yield)
1			
2			
3			
4			
5			
6			

Scheme I

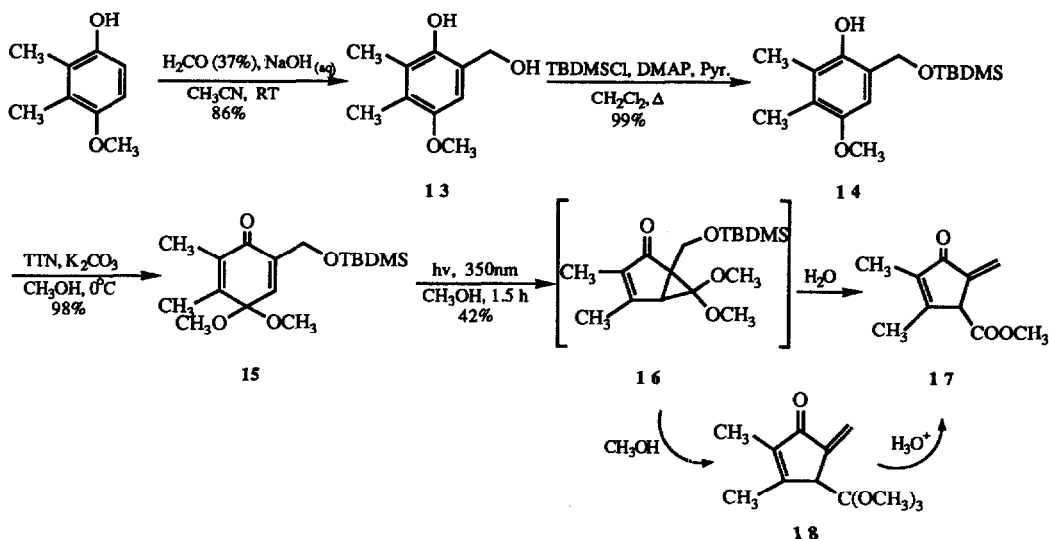


The above-mentioned reactions provide a brief synthesis of 2-cyclopentenones from hydroquinone monomethyl ethers. We applied this synthetic method to prepare methyl ester of (\pm)-desepoxy-4,5-didehydromethylenomycin A (**17**).⁴ 2,3-Dimethylhydroquinone monomethyl ether was converted into **13** by condensation with formalin. Protection of the primary hydroxyl group of **13** with *tert*-butyldimethylsilyl chloride (TBDMSCl) and subsequent oxidation of **14** by TTN afforded masked *p*-benzoquinone **15**. Irradiation of **15** in the above-mentioned manner gave a mixture containing **17** and **18**. Treatment of the irradiated mixture with aqueous ammonium chloride solution followed by chromatography on a silica-gel column yielded **17** in 42% yield.⁹ Bicyclo[3.1.0]hex-3-en-2-one **16** was presumed to be an intermediate in this transformation.

In conclusion, the photochemical rearrangements of alkylated 4,4-dimethoxy-2,5-cyclohexadienones in methanol may serve as an entry to 2-cyclopentenone derivatives that shows different regioselectivities from those of ethylene monoketals of *p*-benzoquinones in acetic acid.^{3c} The effects of other substituents and the nature of protecting groups such as ethylene ketals and *O*-spirolactones⁶ on the photochemical behavior of masked *p*-benzoquinones are under active investigation.

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Scheme II



References and Notes:

1. This is part XII of Chemistry of Benzoquinones and Masked Benzoquinones; for part XI, see Hung, S.-C.; Liao, C.-C. *Tetrahedron Lett.* **1991**, 32, 4011.
2. (a) Schuster, D. I. *Acc. Chem. Res.* **1978**, 11, 65. (b) Schaffner, K.; Demuth, M. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 3, p 281. (c) Schultz, A. G. *Pure Appl. Chem.* **1988**, 60, 981.
3. (a) Hewitt, D. G.; Taylor, R. F. *J. Chem. Soc., Chem. Commun.* **1972**, 493. (b) Margaretha, P. *Helv. Chim. Acta* **1976**, 59, 661. (c) Pirrung, M. C.; Nunn, D. S. *Tetrahedron Lett.* **1988**, 29, 163. (d) Feldman, K. Ph. D. Dissertation, 1984, Stanford University.
4. (a) Hornemann, U.; Hopwood, D. A. *Tetrahedron Lett.* **1978**, 2977. (b) Boschelli, D.; Scarborough, R. M., Jr.; Smith, A. B., III. *Tetrahedron Lett.* **1981**, 19. (c) Koreeda, M.; Chen, Y. P. L. *Tetrahedron Lett.* **1981**, 15. (d) Tius, M. A.; Astrab, D. P.; Fauq, A. H.; Ousset, J.-B.; Trehan, S. *J. Am. Chem. Soc.* **1986**, 108, 3438. (e) Mahidol, C.; Thebtaranonth, C.; Thebtaranonth, Y.; Yenjai, C. *Tetrahedron Lett.* **1989**, 3857.
5. Mckillop, A.; Perry, D. H.; Edwards, M.; Antus, S.; Farkas, L.; Nogradi, M.; Taylor, E. C. *J. Org. Chem.* **1976**, 41, 282.
6. Liao, C.-C.; Wei, C.-P. *Tetrahedron Lett.* **1991**, 32, 4553.
7. Newton, R. F.; Reynold, D. P.; Eyre, T. *Synth. Commun.* **1981**, 11, 527.
8. Ogura, K.; Matsuura, T. *Bull. Chem. Soc. Jpn.* **1970**, 43, 3181 and references cited therein.
9. Spectral data of **17**: ^1H NMR(CDCl_3) δ 1.81(d, $J=2.2\text{Hz}$, 3H), 2.06(s, 3H), 3.71(s, 3H), 4.05(br, 1H), 5.52(d, $J=1.4\text{Hz}$, 1H), 6.12(d, $J=1.4\text{Hz}$, 1H); ^{13}C NMR(CDCl_3) δ 8.5, 15.4, 52.6, 52.6, 117.0, 140.4, 140.6, 160.4, 170.5, 194.3; IR (neat) 3004, 2988, 1740, 1695, 1665, 1638, 1438, 1198, 800, 725 cm^{-1} .

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