# INTRAMOLECULAR PHOTOCYCLOADDITIONS ON DIOXOLENONES: AN EFFICIENT METHOD FOR THE SYNTHESIS OF MEDIUM-SIZED RINGS[1,2]

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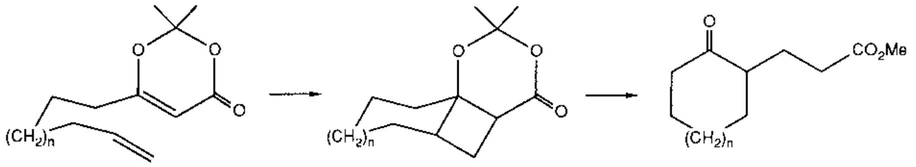
Abstract — The intramolecular photocycloaddition of dioxolenones to simple olefins leads to the formation of six-, seven-, and eight-membered rings in good yields. Asymmetric induction in the formation of cyclooctanes is described.

The extension of the de Mayo reaction[6,7] to the enols of $\beta$-ketoesters could significantly expand the utility of this reaction in synthesis, since the regioselective functionalization, i.e., alkylation and enolization, of the ketoesters is more straightforward than the same transformations in the $\beta$-diketone series.[8,9] Baldwin has reported that dioxolenones, which can be regarded as the covalently restricted cis enol tautomers of the corresponding ketoesters, undergo intermolecular [2+2]-photochemical cycloaddition with alkenes, although with regiochemical outcomes which are difficult to predict.[11] We report herein that the intramolecular photoaddition of dioxolenones to alkenes results in the formation of six-, seven-, and eight-membered rings, i.e, 1→3, in good yields with excellent regiochemical control.

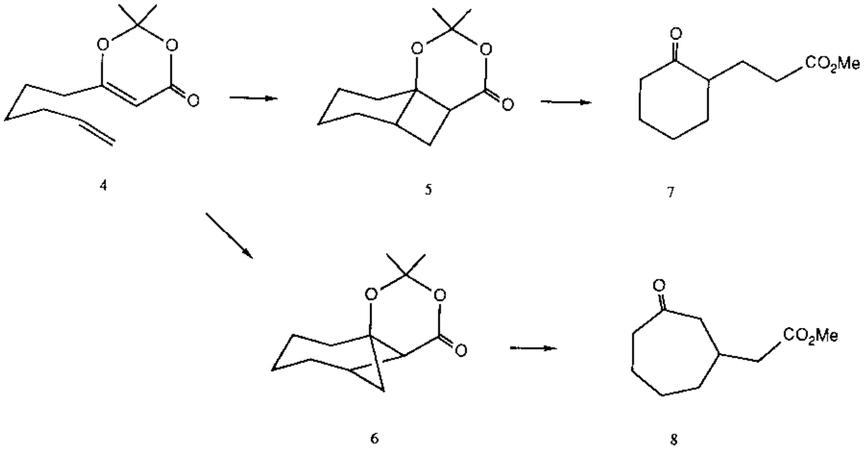
Scheme I



1 2 3 (n = 1, 2, 3)

Photolysis of 4 (0.01M 10% acetone/acetonitrile; 450 W Hg lamp; pyrex filter) could produce two regioisomeric products, 5 or 6 (Scheme II). Fragmentation with p-toluenesulfonic acid in refluxing methanol would then lead to either 7 or 8. In analogy to similar intramolecular reactions in the $\beta$-diketone series,[8,12] we obtained 5 as the major product. Fragmentation of the crude photoproduct under acidic conditions provided a mixture of 7[13] and 8[14] in a ratio of 50:1 (ratio determined by capillary VPC, 73% isolated yield over the two steps).

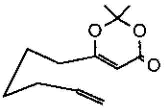
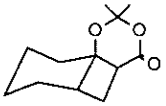
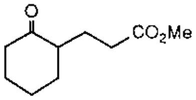
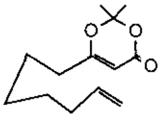
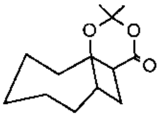
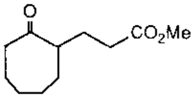
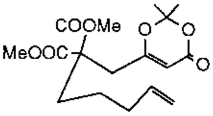
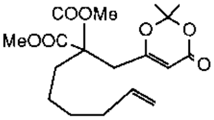
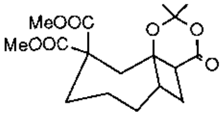
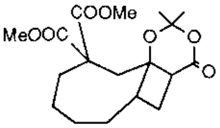
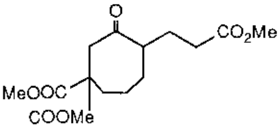
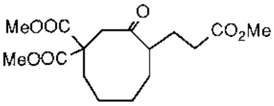
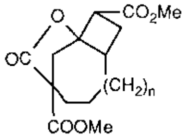
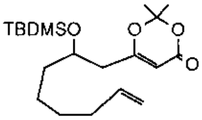
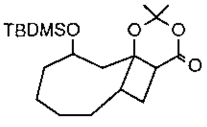
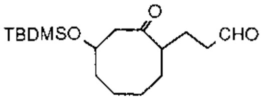
Scheme II



We have also applied this reaction to the synthesis of seven- and eight-membered rings (see the Table). Photoaddition and fragmentation of 9 leads to a single product, 11, in 50% overall yield. None of the isomeric photoproduct could be detected by capillary gas chromatography, establishing a lower limit of ca. 200:1 for the regioselectivity of this photoreaction. The decrease in yield in going from six- to seven-membered rings was expected, but we anticipated that substrates which enjoyed the benefits of the Thorpe-Ingold effect[15] might cyclize more efficiently.

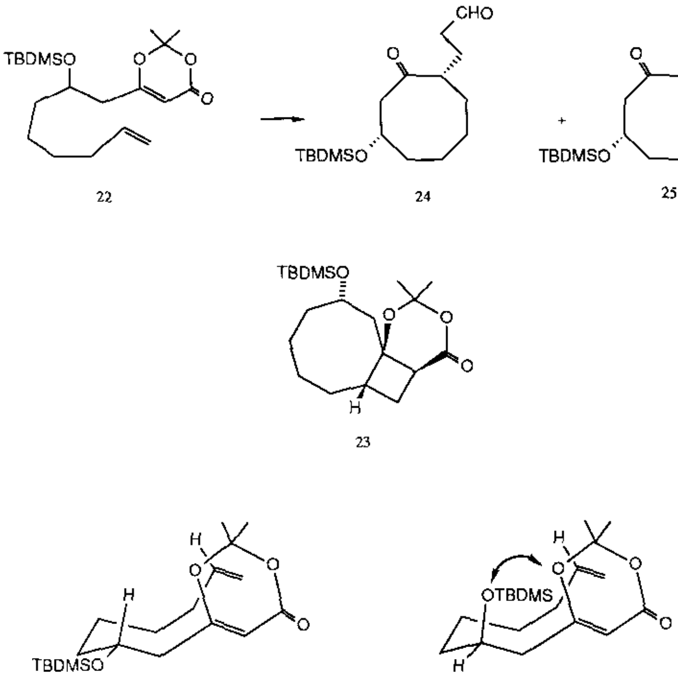
Photolysis of 12 led to photoadduct 13 in 75% yield, and similarly, 15 provided the eight-membered ring photoproduct 16 in 64% yield. Fragmentation of either 13 or 16, respectively, using a catalytic amount of p-toluenesulfonic acid in refluxing methanol, led to the formation of mixtures of the desired ketoesters 14 and 17, along with the lactones, 18 and 19 (85 and 78% combined yields, respectively). However, exposure of 16 to aqueous potassium hydroxide in dioxane (room temperature, 48 h) led to the formation of the triacid corresponding to 17 in quantitative yield.[18]

TABLE[16,17]

| Substrate | Photoadduct | Fragmentation Product |
|---|---|---|
| <br>4 | <br>5 (81) | <br>7 (91) |
| <br>9 | <br>10 (57) | <br>11 (87) |
| <br>12<br><br>15 | <br>13 (75)<br><br>16 (64) | <br>14 (85)<br><br>17 (78)<br><br>18 n=1 19 n=2 |
| <br>22 | <br>23 (55) | <br>24 / 25 (85; cis/trans : 4/1) |

To determine what stereochemical control would be possible in the formation of these eight-membered rings, we next examined the cyclization of the t-butyldimethylsilyl ether 22 (Scheme III). Photoaddition followed by fragmentation with diisobutylaluminum hydride led to a 50% combined yield of 24 and 25 in a 4:1 ratio (determined by NMR). The relative stereochemistry of the major photoadduct 23 was determined by X-ray analysis and is shown below. The preference for the formation of 23 in this reaction can be rationalized by examination of the conformations shown below, in which the eight-membered ring adopts the chair-boat-chair conformation[19]. Conformation A, which avoids the interaction shown in B, leads to 23, in which the oxygens are trans on the eight-membered ring photoproduct.

*Scheme III*



22 24 25

23

A B

The dioxolenone photochemistry has important advantages over the more classical de Mayo diketone sequence. Aside from the benefits of regiochemical control afforded by the use of the $\beta$-ketoesters, this new methodology provides a promising method for achieving stereochemical control in the formation of medium rings. Further experiments designed to enhance the selectivities of these preliminary results, and the application of the intramolecular dioxolenone photocycloaddition to the synthesis of natural products is currently underway in our laboratory.

ACKNOWLEDGEMENTS

We thank Professor Steven Baldwin for helpful discussions. Support from the Petroleum Research Fund, administered by the American Chemical Society, the National Institutes of Health (CA40250 to J.D.W., GM35982 to P.G.W., and GM07148 in the form of a training grant fellowship to J.P.H.), an American Cancer Society Institutional Grant, and Merck, Sharp and Dohme is gratefully acknowledged. The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by the NCI via the University of Chicago Cancer Research Center (CA 14599).

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2. Presented at the 190th National Meeting of the American Chemical Society, Chicago, IL, Sept 8-13, 1985; paper ORGN 205.
3. Recipient of a Merck Grant for Faculty Development, 1985-1986.
4. National Institutes of Health Predoctoral Trainee (GM07148).
5. Address correspondence to this author regarding the X-ray structure of 23.
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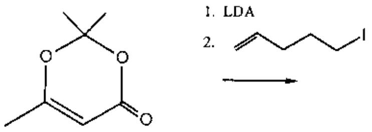
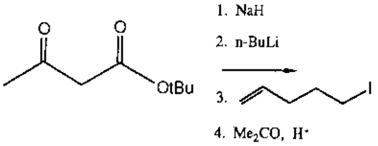
16. Each product exhibited the expected $^1$H-NMR, IR and MS characteristics consistent with the assigned structures. Yields in the Table are noted in parentheses for each photoadduct and fragmentation product, and are based on pure material isolated by chromatography ($SiO_2$).
17. The preparation of photosubstrate 4 was typical of the others and could be done in either of two ways: Alkylation of the known heterocycle i (Ref. 11) with 4-pentenyl iodide (LDA/HMPA/THF) provided substrate 4, albeit in low (20-35%) yield, or dianion alkylation of t-butyl acetoacetate (Ref. 10) with the pentenyl iodide followed by dioxolenone formation (Ref. 20), in two steps, but better (40-60%) overall yield.



4

i



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Received, 12th May, 1986