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Ozonolysis of 1,4-Cyclohexadienes in the Presence of Methanol and Acid. Mechanism and Intermediates in the Conversion of 1,4-Cyclohexadiene Derivatives to β-Keto Esters[1]

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Received February 15, 2004

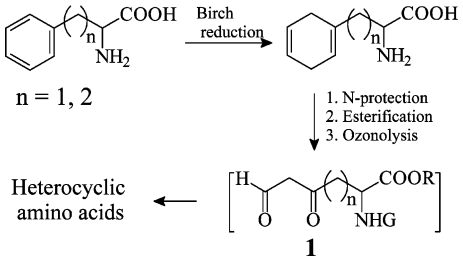
Conditions for the preparation of β-keto esters directly from 1,4-cyclohexadiene derivatives are described. This procedure is a further step in the application of the synthetic methodology, which consists of the combination of Birch reduction of available benzene derivatives followed by ozonolysis. In this work, the syntheses of derivatives of dimethyl γ-keto-α-aminoadipate and dimethyl β-keto glutamate from the corresponding 1,4-cyclohexadiene derivatives are described. The latter compounds are prepared from phenylalanine and phenylglycine, respectively. The study of the ozonolysis of simple alkyl derivatives of 1,4-cyclohexadiene in the presence of methanol, both in the presence and absence of acid, helped to establish the mechanism of this reaction. The proximity of the two double bonds, which are cleaved, leads to the intermediate formation of 1,2-dioxolane derivatives that could be identified by NMR spectroscopy. It is shown that regardless of the regioselectivity of the cleavage of the primary ozonide, which is formed, all 1,2-dioxolane derivatives can lead to β-keto esters. This is due to the equilibrium between these dioxolanes in the presence of methanol and acid.

Introduction

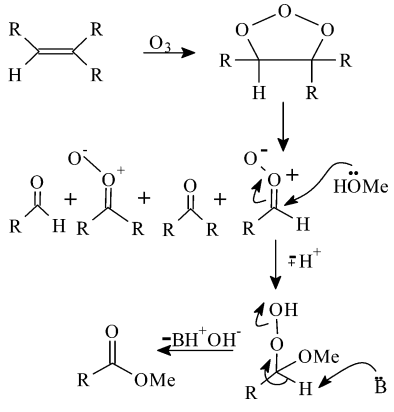
In an effort to develop a methodology for the synthesis of new nonproteinogenic amino acids, we have investigated the transformation of aromatic amino acids such as phenylalanine and phenylglycine to functionalized amino acids by the combination of Birch reduction of the benzene ring, followed by ozonolysis. We have reported previously the synthesis of various new heterocyclic α-amino acids (Scheme 1) by using this methodology.[2−6]

β-Keto esters are important intermediates in organic synthesis. On the other hand, it is well-known that β-keto acids are unstable and undergo a facile decarboxylation. Therefore, it is difficult to achieve these esters by conventional ozonolysis with the intention of further oxidation of the keto aldehyde derivatives (**1**), followed by esterification. One way to overcome this obstacle was described by Evans and co-workers[7] by using a methoxy derivative of 1,4-cyclohexadiene. It is also known that ozonolysis of alkenes in the presence of methanol and base results in the formation of esters directly, without the need of isolation of the carboxylic acid[8] (Scheme 2). The yields in this procedure depend on the regioselec-

SCHEME 1



SCHEME 2



(1) Portions of this investigation were previously presented: Zvilichovsky, G.; Seri, N.; Gbara, I. *The 66th Meeting of The Israel Chemical Society*; Tel Aviv, Israel, February 5−6, 2001; Abstract p 178. Zvilichovsky, G.; Seri, N.; Gbara, I. *The XIXth European Colloquium on Heterocyclic Chemistry*; Aveiro, Portugal, July 19−22, 2000; Abstract p 196. Zvilichvsky, G., Seri, N. *The 65th Meeting of The Israel Chemical Society*; Beer Sheva, Israel, February 8−9, 2000; Abstract p 197.

(2) Zvilichovsky, G.; Gurvich, V. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2509.

(3) . Zvilichovsky, G.; Gurvich, V. *Tetrahedron* **1995**, *51*, 5479.

(4) Zvilichovsky, G.; Gurvich, V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1069.

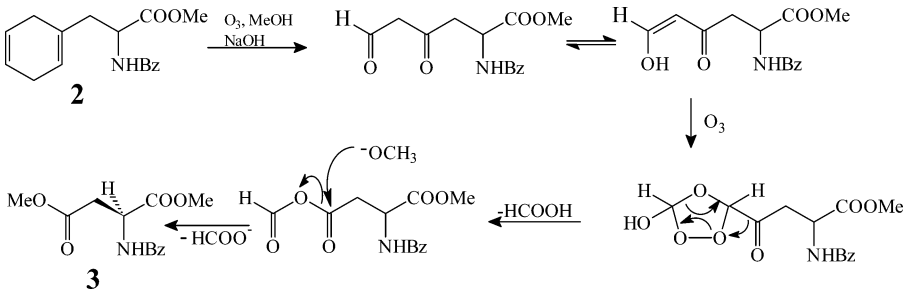
(5) . Zvilichovsky, G.; Gurvich, V. *Tetrahedron* **1997**, *53*, 4457.

(6) Zvilichovsky, G.; Gurvich, V. *Recent Res. Devel. Org. Chem*. **1999**, *3*, 87.

(7) Evans, A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. *J. Org. Chem*. **1991**, *56*, 741.

10.1021/jo049731y CCC: $27.50
Published on Web 05/07/2004

SCHEME 3

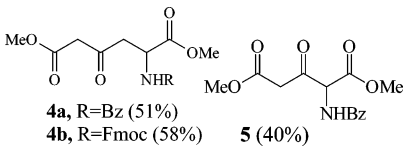


tivity in the cleavage of the primary ozonide. This is because only a carbonyl oxide bearing an adjacent hydrogen can yield an ester. Statistically the maximum yield in such a reaction is 50% (Scheme 2).

The procedure for obtaining esters in which the ozonolysis is carried out in the presence of methanol and base failed in the case of derivatives of 1,4-cyclohexadiene. The ozonolysis of 1,4-cyclohexadienylalanine (**2**) in the presence of methanol and base gave the aspartate ester (**3**). This is probably due to excessive ozonolysis of the enolate species, formation of which is enhanced by base. The loss of a two-carbon chain was explained by the mechanism outlined in Scheme 3 and which was earlier proposed by Bailey.[9] The formation of esters in ozonolysis by using acid catalysis was not hitherto described.

Results and Discussion

In the present work, it was possible to obtain the amino keto adipate and keto glutamate derivatives (**4** and **5**) from phenylalanine and phenylglycine, respectively, by Birch reduction followed by an acid-catalyzed ozonolysis in the presence of methanol. When phenylalanine was used, the products were expected to retain their optical activity.



4a, R=Bz (51%)
4b, R=Fmoc (58%) **5** (40%)

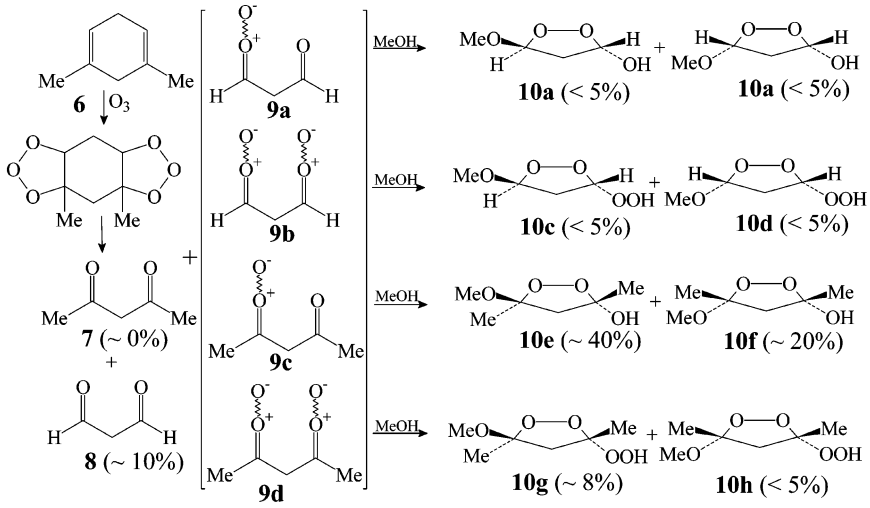
Adding *p*-toluenesulfonic acid provided the acidic media. To avoid excessive ozonolysis, ozone was passed through the chilled solution in the presence of Sudan III as an indicator.[10] The yields were higher than expected from statistical considerations. The formation of an ester in either basic or acidic media requires that the produced carbonyl oxide will be formed at a carbon that bears a hydrogen as shown in Scheme 2. Thus, the ozonolytic process could lead, in the case of a diene like **2**, to only 25% yield if statistical formation of the desired carbonyl oxide was considered. Therefore, it seemed as if there was some regioselectivity in the decomposition of the primary ozonide. To learn more about the regioselectivity it was necessary to apply this ozonolytic procedure to simpler substituted 1,4-cyclohexadienes and try to isolate or identify products and intermediates. By this method, one can learn whether the carbonyl oxide is preferentially formed at the less substituted site. The simplest substrate for such an investigation was 1,5-dimethyl-1,4-cyclohaxadiene (**6**), which was derived by the Birch reduction of 1,3-xylene. At first, the experiments were performed in the absence of acid in order to allow identification of the intermediates. The reactions of the cyclohexadienes with ozone and methanol were run either in methylene chloride or in deuterated chloroform. The latter solvent was used in order to be able to determine the composition of the reaction products and intermediates by NMR before isolation. The ozonolysis in the absence of acid, buffered with $NaHCO_3$ to exclude any acid, which may be generated by oxidation, resulted in the formation of only small amounts of malonaldehyde (**8**), and no acetylacetone (**7**) was detected. Most of the starting material was converted to the cyclic dioxolane derivatives. The proposed structures and estimated product distribution, as determined by proton NMR, are shown in Scheme 4.

Several of the cyclic intermediates could be isolated by silica gel column chromatography as pure products or pairs of isomers and were stable in a test tube for days, enabling the identification by NMR. Traces of all other dioxolanes could be detected in the reaction mixture as well. Elementary analysis, however, was not attempted because of the peroxidic nature of the products. The absence of acetylacetone (**7**) among the products pointed at the preference of the carbonyl oxide moiety to be formed at the branched carbon in of the double bond in 1,5-dimethyl-1,4-cyclohaxadiene (**6**, Scheme 4). However, this regioselectivity was only partial because the major product was the mixture of the two isomers **10e** and **10f**. The trans isomer (**10e**) was the predominant one. This structural assumption is based on the difference in the chemical shift between the two geminal hydrogens. The same preference was found in the peroxidic dioxolanes **10g** and **10h**. Signals above 9 ppm proved to be typical to the hydroperoxy groups.[11] The proposed mechanism for the cyclization of **9** to produce **10** is outlined in Scheme 5.

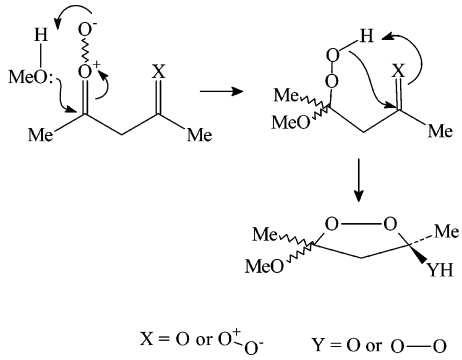
Upon introduction of acid to the ozonolysis mixture, etherification (or ketalization) occurred to produce small amounts of the malonaldehyde tetraacetal (**11**) and the dimethoxydioxolane derivatives (**12** and **13**, Scheme 6). All four products which are presented by the formulas

(8) Ellan, R. M.; Padbury, J. M. *J. Chem. Soc., Chem. Commun.* **1972**, 1086.
(9) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1982; Vol. I, p 159. Hassal, C. H. *Org. React.* **1957**, *9*, 73.
(10) Schreiber, S. L.; Meyers, H. V. *J. Am. Chem. Soc.* **1988**, *110*, 5198. Schreiber, S. L.; Claus. R. E. Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867. Wang, Z.; Zvilichovsky, G. *Tetrahedron Lett.* **1990**, *31*, 5579.
(11) Swern, D.; Clements, A.; Luong, T. M. *Anal. Chem.* **1969**, *41*, 412.

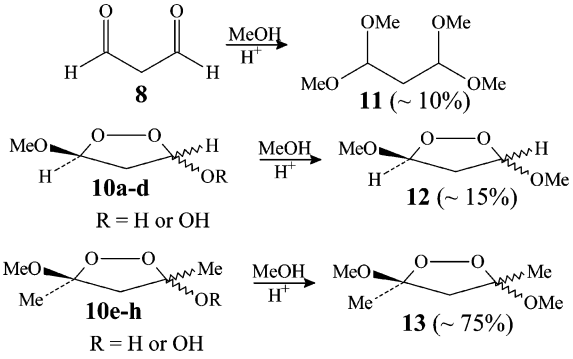
SCHEME 4



SCHEME 5



SCHEME 6

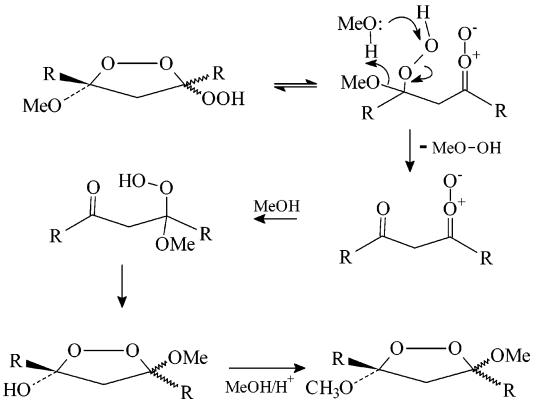


12 and **13** were observed in the reaction mixture. The product distribution (Scheme 6) indicated the predominance of the dioxolanes bearing the two methyl groups (about 75%). Partial purification of one isomer (**13a**) was achieved by column chromatography.

Both the hydroxy groups and the hydroperoxy groups in **10** were converted by acid in the presence of methanol to methoxy groups. The suggested mechanism for the conversion of the hydroperoxy group into the hydroxy group (Scheme 7) is in agreement with previous findings, although MeOOH would not be considered as a good leaving group.[12]

The above experiments still did not explain the formation of the keto esters (**4** and **5**) in yields of about 50%. The observed predominance of products **10e**−**h** indicated

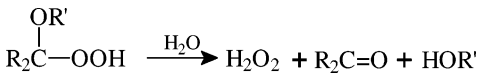
SCHEME 7



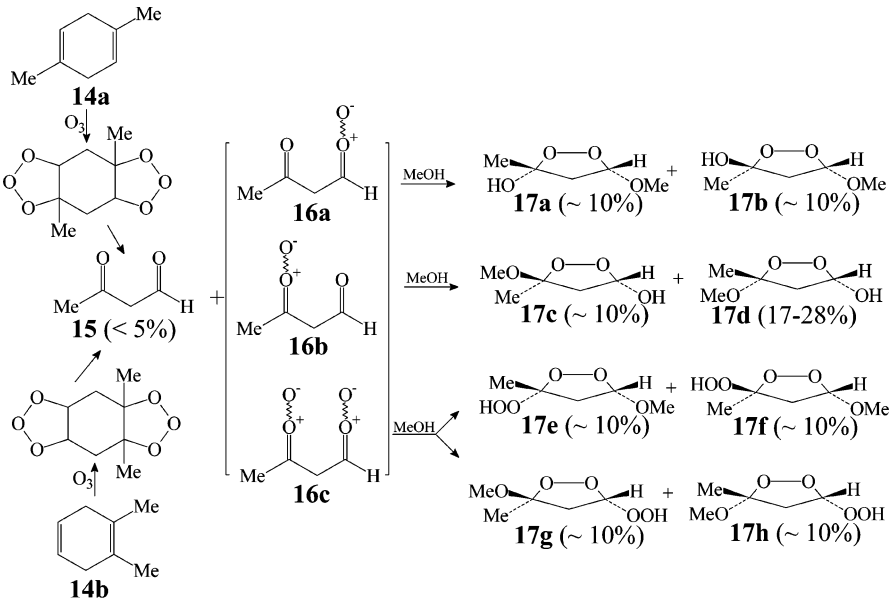
that the more substituted carbonyl oxides **9c** and **9d** are the preferred decomposition products of the primary ozonide. This trend should bring about a lower yield of an ester than the statistical 25% because an ester group is only produced when the carbonyl oxide is attached to a carbon that bears a hydrogen. Therefore, it was advisable to use 1,4-cyclohexadiene derivatives that can yield keto esters. Thus, 1,4 and 1,2-dimethyl-1,4-cyclohexadienes were chosen, where in this type of ozonolysis, they should lead to ethyl acetoacetate exclusively, provided that the less substituted carbon is converted to the carbonyl oxide moiety. This is because it is necessary for the formation of an ester group that a hydrogen is present on the same carbon as the carbonyl oxide group, as shown in Scheme 2 and in Scheme 9 below. The results of the treatment of these two dienes with ozone as above without acid, as observed in the ^{1}HNMR spectra, showed the pattern summarized in Scheme 8. Signals arising from all the dioxolanes **17a**−**h** were detected.

There were only traces of 3-oxobutyraldehyde (**15**) observed after partial separation by column chromatog-

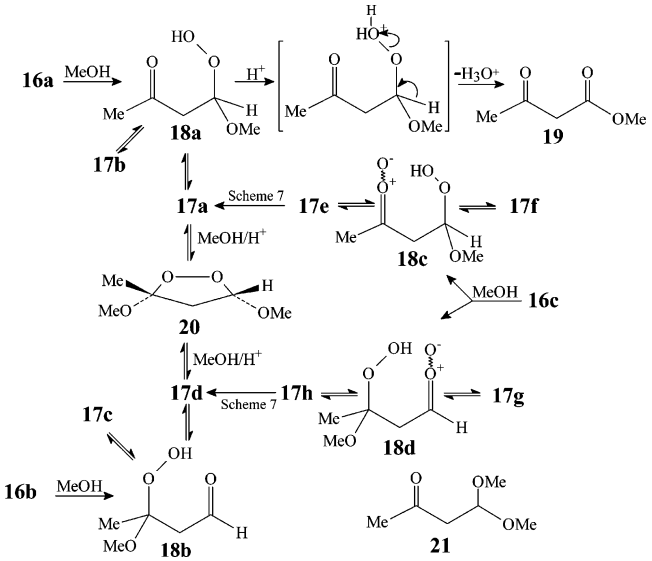
(12) Subulsky and co-workers (Subulsky, L. A.; Harris, G. C.; Maggiolo, A.; Tumolo, A. A. *Adv. Chem. Ser.* **1959**, *21*, 149) have mentioned the formation of hydrogen peroxide in the decomposition of alkoxyperoxides to ketones. The MeOOH is probably as bad a leaving group as HOOH.



SCHEME 8



SCHEME 9



raphy. Partial separation into pairs of isomers was possible, and all cyclic (**17a**−**h**) derivatives were observed in about equal amounts (∼10%), as shown in Scheme 8, or rather a slight predominance of **17d** (17−28%). Upon treatment with ozone in the presence of acid and methanol, both **14a** and **14b** gave a small amount of the diacetal (**21**, Scheme 9), and the dimethoxydioxolane derivative (**20**) was the predominant cyclic product as observed by ^{1}HNMR.

However, upon sitting at room temperature in the acidic medium, the amount of the latter dioxolane (**20**) decreased with time and the formation of methyl acetoacetate (**19**) was observed. This change continued until all of **20** was converted into methyl acetoacetate. These phenomena were explained by the equilibrium that exists, in the presence of methanol and acid, between all the cyclic dioxolanes with the open-chain hydroperoxides (**18a**−**d**), which leads to probably the most stable isomer **20** (Scheme 9). The irreversible step that leads to methyl acetoacetate (**19**), by the mechanism shown in Scheme 9, leads finally to better yields regardless of the regioselectivity and whether the carbonyl oxide which was formed is **16a**, **16b,** or **16c**. The hydroperoxydioxolanes (**17g** and **17h**) will also enter into this dynamic cycle by a similar process (Scheme 7), leading to the *β*-ketoester (Scheme 9).

In conclusion, the mechanism for the formation of *β*-keto esters such as **4** and **5** from 1,4-cyclohexadienylalanine and 1,4-cyclohexadienylglycine by ozone, in the presence of methanol and toluenesulfonic acid, is better understood. Regardless of the regioselectivity of the decomposition in the primary ozonide, the formation of three of the possible carbonyl oxides (analogues of **16a**, **16b**, and **16c**) will eventually lead to the *β*-keto esters, like in the formation of methyl acetoacetate (**19**) in Scheme 9. The preparation of new derivatives of *β*-keto esters from phenylalanine and phenylglycine is described here as well.

Experimental Section

Preparation of Dimethyl S-*N*-Benzoyl-2-amino-4-oxoadipate (4a) by Ozonolysis of Methyl S-*N*-Benzoyl-3-(1,4-cyclohexadien-1-yl)alaninate. Methyl S-*N*-benzoyl-3-(1,4-cyclohexadien-1-yl)alaninate, which was prepared by the Birch reduction of l-phenylalanine, followed by *N*-benzoylation and esterification[2,3] (1.0 g, 3.5 mmol), was dissolved in dichloromethane (25 mL). *p*-Toluenesulfonic acid (0.2 g, 1.1 mmol), 5 mL of methanol, and a drop of a methanolic solution of Sudan III indicator were added. The dilution of the indicator solution was adjusted so that the reaction mixture will have a very slight pink color. The solution was cooled on an acetone dry ice bath (−78 °C), and a mixture of ozone and oxygen was passed carefully until the light pink color faded. After the mixture sat for 72 h at room temperature, the solvent was evaporated to a small volume and the residue loaded on a silica gel column. Upon elution with petroleum ether−ethyl acetate gradient the keto ester dimethyl S-*N*-benzoyl-2-amino-4-oxoadipate **(4a)** was obtained: yield 0.55 g (51%); mp 112 °C; $[\alpha]^{25}_D = +324$ ($CHCl_3$, $c = 10$); ^{1}HNMR ($CDCl_3$, 400 MHz) δ 7.77 (dd, $J = 7.1$, 1.6 Hz, 2H), 7.52 (dt, $J = 7.4$, 1.6 Hz, 1H), 7.44 (t, $J = 7.4$ Hz, 2H), 7.02 (d, $J = 7.4$ Hz, 1H), 5.01 (dt, $J = 7.7$, 4.2 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.48 (s, 2H), 3.40 (dd A part of AB system, $J = 18.5$, 4.2 Hz, 1H), 3.27 (dd

B part of AB system, $J = 18.5$, 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 201.6, 171.6, 167.4, 167.3, 133.9, 132.3, 129.0, 127.6, 53.3, 52.9, 49.2, 49.0, 44.7. Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.38; H, 5.74; N, 4.17.

Preparation of Dimethyl S-*N*-(9-Fluorenylmethoxycarbonyl)-2-amino-4-oxoadipate (4b) by Ozonolysis of Methyl S-*N*-(9-Fluorenylmethoxycarbonyl)-3-(1,4-cyclohexadien-1-yl)alaninate. Methyl S-*N*-(9-fluorenylmethoxycarbonyl)-3-(1,4-cyclohexadien-1-yl)alaninate, which was prepared by the Birch reduction of L-phenylalanine, followed by reaction with *N*-(9-fluorenylmethoxycarbonyl)succinimide and esterification[2,3] (0.5 g, 1.2 mmol) was dissolved in dichloromethane (20 mL). *p*-Toluenesulfonic acid (0.1 g, 0.5 mmol), 3 mL of methanol, and a drop of a methanolic solution of Sudan III indicator were added. The dilution of the indicator solution was adjusted so that the reaction mixture will have a very slight pink color. The solution was cooled and treated as above. Upon elution with petroleum ether−ethyl acetate gradient the keto ester dimethyl S-*N*-(9-fluorenylmethoxycarbonyl)-2-amino-4-oxoadipate **(4b)** was obtained: mp 123 °C; yield 0.3 g (58%); $[\alpha]^{25}_D = -30.2$ ($CHCl_3$, $c = 8$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, $J = 7.4$ Hz, 2H), 7.59 (d, $J = 7.3$ Hz, 2H), 7.4−7.2 (m, 4H), 5.80 (d, $J = 8.4$ Hz, 1H), 4.6 (dd, $J = 8.5$, 4.3 Hz, 1H), 4.38 (m, 2H**)**, 4.22 (t, $J = 7.0$ Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.44 (s, 1H), 3.16 (dd A part of AB system, $J = 18.4$, 4.3 Hz, 2H) 3.32 (dd B part of AB system, $J = 18.4$, 4.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 201.2, 171.6, 167.4, 156.4, 144.23, 144.1, 141.7, 128.2, 127.5, 125.6, 120.4, 67.7, 53.3, 52.9, 50.2, 49.3, 47.5, 45.0. Anal. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29. Found: C, 65.07; H, 5.48; N, 3.11.

Preparation of Racemic Dimethyl *N*-Benzoyl-3-oxoglutamate (5) by Ozonolysis of Methyl R-*N*-Benzoyl-2-(1,4-cyclohexadien-1-yl)glycinate. Methyl R-*N*-benzoyl-2-(1,4-cyclohexadien-1-yl)glycinate, which was prepared by the Birch reduction of d-phenylglycine, followed by *N*-benzoylation and esterification[2,3] (1.0 g, 3.7 mmol) was dissolved in dichloromethane (25 mL). *p*-Toluenesulfonic acid (0.2 g, 1.1 mmol), 5 mL of methanol, and a drop of a methanolic solution of Sudan III indicator were added. The dilution of the indicator solution was adjusted so that the reaction mixture had a very slight pink color. The solution was cooled and treated as above. Upon elution with petroleum ether−ethyl acetate gradient the keto ester dimethyl *N*-benzoyl-3-oxoglutamate (**5**) was obtained: yield 0.43 g (40%); mp 96 °C; $[\alpha]^{25}_D = \sim 0$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.84 (d, $J = 7.5$ Hz, 2H), 7.53 (t, $J = 7.5$ Hz, 1H), 7.42 (t, $J = 7.5$ Hz, 2H), 5.63 (d, $J = 6.7$ Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.70 (s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 194.5, 169.2, 167.4, 167.1, 166.6, 134.0, 133.1, 129.1, 127.7, 56.11, 53.8, 53.0, 47.0. Anal. Calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.46; H, 5.31; N, 4.80.

General Procedure for Treatment of 1,4-Cyclohexadienes with Ozone in the Presence of Methanol in Dichloromethane. A 1,4-cyclohexadiene (0.42 g, 4 mmol) was dissolved in dichloromethane (10 mL), and 1.5 mL (40 mmol) of methanol, 0.08 g of $NaHCO_3$, and a drop of a methanolic solution of Sudan III indicator were added. The indicator solution was adjusted so that the reaction mixture had a very slight pink color. The solution was cooled on an acetone−dry ice bath (−78 °C), and a mixture of ozone and oxygen was passed carefully until the light pink color faded. The solvent was evaporated to a small volume (1 mL) and loaded on a silica gel column. Identification of fractions was performed on TLC, viewing the spots by immersion of either KI solution or ethanolic anisaldehyde (1% aldehyde and 1% H_2SO_4), on different plates. The KI solution detected the hydroperoxides (brown-yellow coloration), but upon standing at room temperature yellow stains of the hydroxydioxolanes were observed as well. The anisaldehyde solution was used to detect hydroxydioxolanes and carbonylic compounds (blue and red coloration). Elution was carried out with petroleum ether−ethyl acetate gradient, and the NMR spectra were taken immediately.

General Procedure for Treatment of 1,4-Cyclohexadienes with Ozone in the Presence of Methanol and *p*-Toluenesulfonic Acid in Dichloromethane. A 1,4-cyclohexadiene (0.42 g, 4 mmol) was dissolved in dichloromethane (10 mL), and 1.5 mL (40 mmol) of methanol, *p*-toluenesulfonic acid (0.05 g, 0.3 mmol), and a drop of a methanolic solution of Sudan III indicator were added. The dilution of the indicator solution was adjusted so that the reaction mixture had a very slight pink color. The solution was cooled on an acetone−dry ice bath (−78 °C), and a mixture of ozone and oxygen was passed carefully until the light pink color faded. The solvent was evaporated to a small volume (1 mL) and loaded on a silica gel column. Identification of fractions was performed on TLC, as above. All products gave color with the anisaldehyde solution. Dimethoxyoxolanes gave yellow color with KI solution, only after it was immersed in 1% ethanolic H_2SO_4. Elution was carried out with petroleum ether−ethyl acetate gradient, and the NMR spectra were taken immediately.

General Procedure for Treatment of 1,4-Cyclohexadienes with Ozone in the Presence of Methanol in $CDCl_3$. A 1,4-cyclohexadiene (0.1 g, 1 mmol) was dissolved in $CDCl_3$ (2 mL), and 0.35 mL (10 mmol) of methanol, and a drop of a methanolic solution of Sudan III indicator were added. The indicator solution was adjusted so that the reaction mixture had a very slight pink color. The solution was cooled on an acetone−dry ice bath (−78 °C), and a mixture of ozone and oxygen was passed carefully until the light pink color faded. The reaction mixture was thus ready for taking the NMR spectrum.

General Procedure for Treatment of 1,4-Cyclohexadienes with Ozone in the Presence of Methanol and *p*-Toluenesulfonic Acid in $CDCl_3$. A 1,4-cyclohexadiene (0.1 g, 1 mmol) was dissolved in $CDCl_3$ (2 mL), and 0.35 mL (10 mmol) of methanol, *p*-toluenesulfonic acid (0.01 g, 0.06 mmol), and a drop of a methanolic solution of Sudan III indicator were added. The indicator solution was adjusted so that the reaction mixture had a very slight pink color. The solution was cooled on an acetone−dry ice bath (−78 °C), and a mixture of ozone and oxygen was passed carefully until the light pink color faded. The reaction mixture was thus ready for taking the NMR spectrum.

Supporting Information Available: A report on improved Birch reduction of xylenes, the description of the ozonolysis of methyl S-*N*-benzoyl-3-(1,4-cyclohexadien-1-yl)-alaninate (**2**) in the presence of methanol and base, copies of the ^{1}H NMR spectra of mixtures and partly isolated dioxolanes, and copies of ^{1}H and ^{13}C NMR spectra of **4a**,**b** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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