

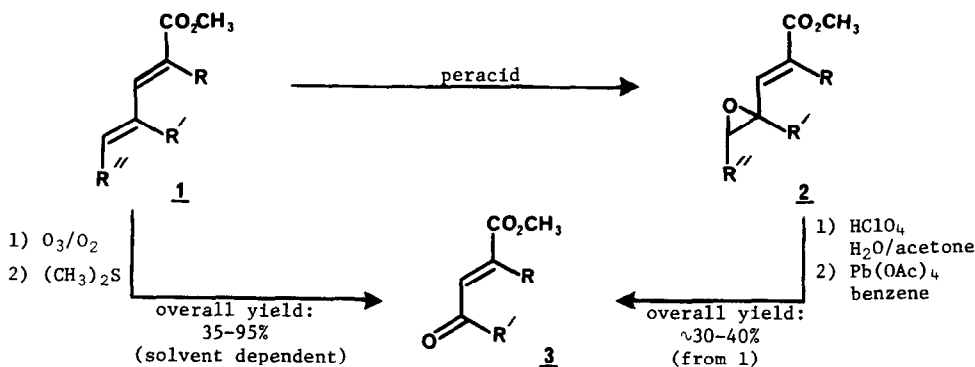
SELECTIVE OZONOLYSIS OF 2,4-DIENOATE ESTERS: A CONVENIENT STEREOSELECTIVE PREPARATION OF 4-OXO AND 4-HYDROXY TRANS-2-ALKENOATES

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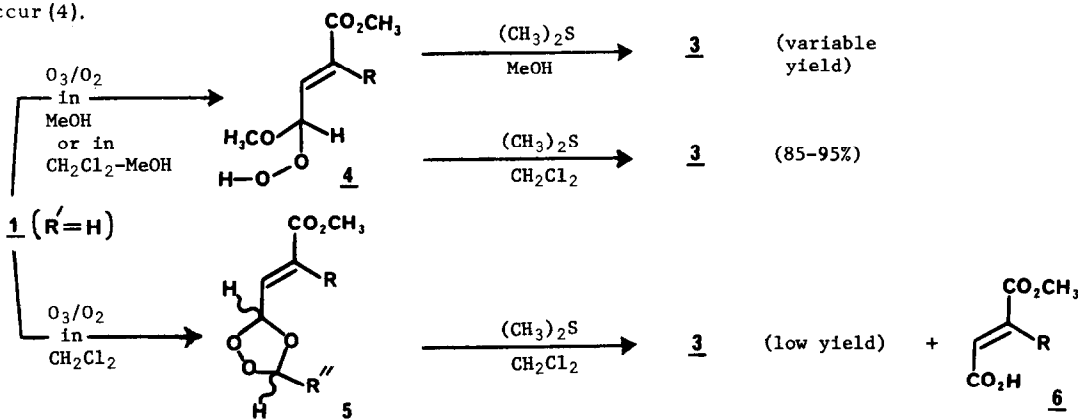
The highly, but selectively, functionalized structures, 4-oxo- and 4-hydroxy-2-alkenoates of known trans double bond stereochemistry, may be of value to the synthetic organic chemist as acyclic olefin synthons and as unusual Diels-Alder dienophiles. In looking for some efficient preparations of these potentially useful intermediates, we anticipated a simple and rapid preparation based on the oxidative cleavage of alka-2,4-dienoates 1. We recalled the reported selective epoxidation and subsequent cleavage at the Δ^4 -double bond of methyl sorbate 1a ($R=R'=H$, $R''=CH_3$) and methyl 2-methylsorbate 1b ($R'=H$, $R=R''=CH_3$), as detailed by A. M. Hudrlík (1), and concluded that a more efficient and, perhaps, higher yield oxidative cleavage might be effected via ozonolysis. That highly electrophilic ozone should selectively attack the Δ^4 unsaturation of 2,4-dienoates seemed, a priori, a likely possibility in view of the lower electron density expected at the Δ^2 -olefin (directly π -conjugated with, and σ -induced by, an electron-withdrawing carbonyl substituent). In this regard, one of us noted some time ago (2) that ozonolysis (1 eqt. O_3) of methyl sorbate 1a in methanol (1:10 w/w) at $-25^\circ C$ followed by reduction with dimethyl sulfide did indeed produce methyl fumaraldehyde 3a (methyl trans-4-oxo-2-butenoate) but only in ~ 35 -40% isolated yield. Slightly improved yields resulted when the aldehyde was first isolated and purified as its dimethyl acetal and subsequently hydrolyzed to 3a. However, in these ozonolyses no products derived from crotonaldehyde (from Δ^2 initial ozonolytic attack) were observed, using either work-up.



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We have reinvestigated the ozonolysis of compounds 1 and can now report that ozonolytic oxidative cleavage is, indeed, highly selective at the Δ^4 -olefin, producing the desired 4-oxo-2-alkenoates 3 in excellent yield. Although when carried out in methanol or methylene chloride, the ozonolysis-reduction sequence often gave only moderate yields of 3 from 1, excellent results were generally observed when a standardized stream of ozone (1 eqt.) in oxygen was passed into a solution at -30°C of ester 1 in methylene chloride containing slightly more than one equivalent methanol. Apparently, in polar hydroxylic solvents such as methanol, the expected methoxy hydroperoxide 4 (when $\text{R}'=\text{H}$) may undergo further reaction before reduction to 3 can be effected; alternatively, in less polar, non-hydroxylic solvents such as methylene chloride, ozonide 5 ($\text{R}'=\text{H}$), formed as a mixture of geometric isomers (3), is apparently quite stable and reduces only quite slowly using excess dimethyl sulfide—so slowly that disproportionation leading to 6 competes with reduction. Our results with mixed solvent system suggest that 4 is produced in methylene chloride if methanol is present and that secondary reactions of 4 are inhibited in methylene chloride; however, 4 can nevertheless be rapidly reduced in this solvent using excess dimethyl sulfide before any complicating side reactions occur (4).



In Table I are summarized the yields of 4-oxo-2-alkenoates 3 (5) obtained from several esters 1 (6, 7) under a variety of conditions. When esters 1 were pure trans Δ^2 -olefins (via the method of synthesis or derived from fractionally recrystallized Δ^2 -trans dienoic acids), the products 3 were obtained as pure trans olefins. That equilibration of double bond geometry is unlikely during ozonolysis or work-up was shown by the formation of a 15:85 cis/trans mixture of 3b from a 1:2 Δ^2 -cis/trans mixture of 1b. It is interesting, however, that the cis isomer was extensively destroyed during the ozonolysis, perhaps by formation of a peroxy lactone or cyclic ozonide, such as 7 or 8, which may subsequently undergo further ozonolysis or oxidative collapse to pyruvate esters.

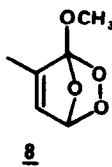
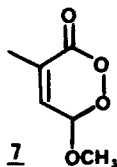
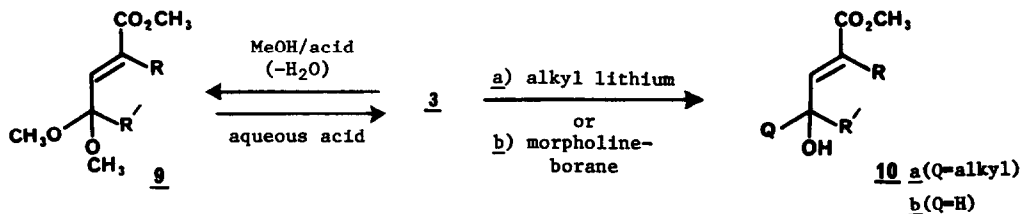


Table 1

starting dienoate <u>1</u> (<u>trans</u> , <u>trans</u> —except as noted)	product <u>3</u> (<u>trans</u> —except as noted)	ozonolytic cleavage method	percent yield
<u>1a</u> methyl sorbate (R''=CH ₃ , R=R'=H)	<u>3a</u> methyl fumaraldehyde (R=R'=H)	A	>95 ^a
		B	35 ^a
		C	45 ^{a, b}
		D	50 ^a
<u>1b</u> methyl 2-methylsorbate (R=R''=CH ₃ , R'=H)	<u>3b</u> methyl 2-methylfumaraldehyde (R=CH ₃ , R'=H)	A	85 ^c
		B	~65 ^d
<u>1b</u> (as a 1:2 mixture of Δ^2 - <u>cis</u> and <u>trans</u>)	<u>3b</u> (mixture Δ^2 - <u>cis</u> and <u>trans</u>)	A	64 ^e (ratio of <u>cis-3b</u> : <u>trans-3b</u> = 15:85)
<u>1c</u> methyl 4-methyl-2,4-pentadienoate (R'=CH ₃ , R=R''=H)	<u>3c</u> methyl 4-oxopent-2-enoate (R=H, R'=CH ₃)	A	>86 ^f
Methods:			
A addition at -30°C of 1 eqt. O ₃ in O ₂ to <u>1</u> in CH ₂ Cl ₂ containing 1-1½ eqt. MeOH; subsequent addition of excess dimethylsulfide; aqueous bicarbonate work-up			
B addition at -30°C of 1 eqt. O ₃ in O ₂ to <u>1</u> in MeOH; subsequent addition of excess dimethylsulfide; evaporation of volatile materials and aqueous bicarbonate work-up			
C addition at -30°C of 1 eqt. O ₃ in O ₂ to <u>1</u> in CH ₂ Cl ₂ ; subsequent addition of excess dimethylsulfide; aqueous bicarbonate work-up			
D addition at -30°C of 1 eqt. O ₃ in O ₂ to <u>1</u> in MeOH; subsequent addition of excess dimethylsulfide; subsequent conversion to and isolation (hexane extract) of the dimethyl acetal (using methanol, catalytic acid, and Na ₂ SO ₄); hydrolysis of the acetal (using cold aqueous acid in THF)			
^a Aqueous bicarbonate soluble by-products were not investigated; no crotonaldehyde or any product derived from it was observed (nmr).			
^b Fumaric acid monomethyl ester <u>6</u> was isolated from the aqueous bicarbonate washes.			
^c Methyl pyruvate (~10%) was identified (nmr, glc); no crotonaldehyde or any product derived from it was observed (nmr).			
^d Methyl pyruvate (~20%) was identified (nmr); no crotonaldehyde or any product derived from it was observed (nmr).			
^e Based on the amount of each isomer present in the <u>cis</u> , <u>trans</u> mixture of <u>1b</u> and on the 85% yield of <u>trans-3b</u> from <u>trans-1b</u> , calculated yield of <u>cis-3b</u> from <u>cis-1b</u> is 31%; the significant quantities of methyl pyruvate (>28%) apparently result from over-oxidation of <u>cis-1b</u> or its ozonolysis products.			
^f Aqueous bicarbonate soluble by-products were not investigated; no methacrolein or any product derived from it was observed (nmr).			

Unlike the substituted dienoate ozonolyses reported in Table 1, esters of the parent pentadienoic acid (R=R'=R''=H) consistently gave low yields of 3a, even when ozonized in a methanol/methylene chloride mixed solvent system; however, these results were not completely unexpected since monosubstituted alkenes are not particularly electron-rich; consequently, it is not unreasonable to expect competitive electrophilic attack at Δ^2 double bond to occur. Although in the ozonolysis of trans-1b small amounts of pyruvate esters (~10%) were observed, no crotonaldehyde or methacrolein has thus far been detected as products of the reactions in Table 1 (see footnotes 7 and 8).

We have also observed that compounds 3 are readily converted to their 4,4-dimethoxy derivatives 9 (methanol, trace acid, drying agent at room temperature for 24-48 hours)



without any apparent double bond equilibration. And, finally, compounds 3 readily undergo selective nucleophilic addition to the C-4 aldehyde or ketone using one equivalent of alkyl lithium(9) reagents at -70° , producing the expected γ -alkyl- γ -hydroxy alkenoates 10a in greater than 85% yield; similarly, morpholine borane in methanol converted 3 to the expected allylic alcohols 10b in greater than 85% yield.

It should be apparent that these transformations make compounds 3, 9, and 10 readily available from starting dienoate esters 1. Since esters 1 are prepared from easily accessible precursors, this selective ozonolysis sequence conveniently provides 4-oxo-, 4,4-dimethoxy, and 4-hydroxy-trans-2-alkenoates for use as synthetic intermediates.

Acknowledgements

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References and Footnotes

1. A. M. Hudrlik, Ph.D. Thesis, Columbia University, New York, N. Y., 1967.
2. P. L. Stotter, Ph.D. Thesis, Columbia University, New York, N. Y., 1968.
3. After solvent was removed in vacuo at room temperature, the oily ozonide residues exhibit 60 and 100 MHz nmr spectra consistent with a complex mixture composed largely of geometric isomers 5 ($R=R'=H$, $R''=CH_3$), ratio $\sim 3:2$, and some aldehyde 3a.
4. (a) Excess dimethyl sulfide(4b), added at -30° , was used as reducing agent in all ozonolysis-reduction procedures described in Table 1. Stirring of the reaction mixture at room temperature was maintained (18-72 hrs.) until all ozonides or peroxides were reduced (no oxidation of KI/starch).
(b) J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).
5. Products 3 were identified by comparison with authentic samples or by careful correlation of spectral data and physical constants with those reported in ref. 1 and ref. 2, as well as in the following.
(a) R. Rambaud and M. Vessiere, *Bull. Soc. Chim., France*, 1957 (1961).
(b) H. -J. Bestmann, G. Graf, and H. Hartung, *Ann. Chem.*, 706, 68 (1967).
6. (a) Methyl sorbate 1a was prepared from the commercially available acid as reported by A. B. Sen and V. S. Misra, *J. Indian Chem. Soc.*, 26, 149 (1949).
(b) Dienoates 1b and 1c were most conveniently prepared via standard Wittig and/or Emmons procedures using α -carbalkoxy phosphoranes or phosphonates with crotonaldehyde or methacrolein. Dienoate 1c was isolated directly as the trans,trans-isomer. Isomerically pure 1b was easily derived by hydrolysis of the crude ester mixture (Δ^2 -trans/ Δ^2 -cis $\sim 9:1$), recrystallization of the known trans,trans-acid(6c), and esterification of the pure acid with diazomethane.
(c) K. V. Auwers and J. Heyna, *Ann. Chem.*, 434, 157 (1923).
7. Comparable results have been obtained for ozonolyses of t-butyl esters corresponding to methyl esters 1 listed in Table 1.
8. (a) Additional alkyl substituents on the Δ^4 double bond do not increase yields of 3, despite the greater electron density expected in this trisubstituted double bond. Apparently, "indirect" steric factors become dominant in the ozonolysis transition state(8b) and decrease positional selectivity. When methyl 2,5-dimethylsorbate was ozonized (method A), a mixture (2:1) of 3b and methyl pyruvate was obtained; some β,β -dimethylacrolein was also observed (nmr).
(b) D. G. Williamson and R. J. Cveticovic, *J. Amer. Chem. Soc.*, 90, 3668, 4248 (1968).
9. Compare with 48% yield using Grignard reagents, as reported by J. F. Laporte and R. Rambaud, *C. R. Acad. Sci., Paris, Ser. C.*, 252, 1095 (1966).