Table V. Normalized Relative Rates at pH 8.0, 0.0250 M KI

1-thia-5-oxacyclooctane (5-oxathiocane)[22]	1
1-thia-6-oxacyclodecane (6-oxathiotane)[22]	3
thiacyclooctane (thiocane)[13]	40
1-methyl-2-[2-(methylthio)ethyl]benzimidazole, 3	700
2-[2-(methylthio)ethyl]benzimidazole, 2	1600
2-[2-(methylthio)ethyl]pyridine[15]	1600
1-methyl-2-[3-(methylthio)propyl]benzimidazole, 5	100000
2-[3-(methylthio)propyl]benzimidazole, 4	200000
1-methyl-2-[3-(methylthio)propyl]imidazole, 1	2000000

N-5 and N-6 participation from what it would be in the analogous acyclic cases. Additionally, the geometry of the imidazole ring is such that N-5 participation produces a considerably more strained intermediate than N-6 participation, primarily as a result of the rigid angular constraint of the sp^2 hybridized atoms. Similar results have been reported when unsaturation is introduced into the system.[20a] Knowledge of $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ for the cyclization step would be illuminating; however, only the overall, composite values (which include the preequilibria as well) can be determined.

The rate acceleration observed upon changing from a benzimidazole nucleus to an imidazole nucleus is to be expected. Inductive electron withdrawal by the benzene ring is the primary cause of the greater nucleophilicity of imidazole relative to benzimidazole.[21] The difference in this case (a factor of 20—see Table V) is not great and is smaller at lower iodide concentrations. In light of the difference in mechanism, not too much significance should be attributed to it. Additionally, solvation effects undoubtedly play a role since 1 is highly water soluble while 5 is only slightly soluble.

In a similar fashion (comparing 5 with 4 and 3 with 2), the small increase (~2-fold) observed upon changing the substitution at the imino nitrogen from methyl to hydrogen is likely due to differences in solvation and is not particularly significant. The presence of the imino hydrogen provides the opportunity for hydrogen bonding that is not otherwise available.

Relative Rate Summary. In Table V is a listing of the relative oxidation rates for a number of thioethers studied in this laboratory. Each of these compounds has essentially an inverse second-order dependence in iodide, with the −3 order for the buffer independent path in the oxidation of 5 being the most notable deviant.

The rates have been normalized to pH 8.0 at an iodide concentration of 0.0250 M. The rates are extrapolated to zero buffer where appropriate. Finally, the relative concentrations have been adjusted in accordance with the observed pK_a and the pH where appropriate.

The cyclic ether thioethers[22] are obviously the most sluggish of the lot. The rate differences between the ether thioethers and thiocane (thiacyclooctane) border on the insignificant. The anchimeric assistance provided by the benzimidazole and imidazole groups, however, ranges from moderate (in the case of N-5 participation in the benzimidazoles) to quite dramatic in the case of N-6 participation. Clearly neighboring-group participation by imidazole (via histidine residues) has the potential for catalyzing similar redox processes in biological systems.

Acknowledgment. This research was supported by The National Science Foundation and The National Institutes of Health.

Registry No. 1, 93530-04-2; 1 (sulfoxide), 93530-10-0; 2, 4198-64-5; 2 (sulfoxide), 93530-11-1; 3, 93530-05-3; 3 (sulfoxide), 93530-12-2; 4, 93530-06-4; 4 (sulfoxide), 93530-13-3; 5, 93530-07-5; 5 (sulfoxide), 93530-14-4; 3-chloropropyl methyl sulfide, 13012-59-4; 3-iodopropyl methyl sulfide, 93530-08-6; *N*-methylimidazole, 616-47-7; *N*-methyl-*o*-phenylenediamine, 4760-34-3; 3-(methylthio)propionic acid, 646-01-5; 4-(methylthio)butyric acid, 32391-97-2; *o*-phenylenediamine, 95-54-5; potassium *o*-nitroaniline *p*-toluenesulfonanilide, 93530-09-7; *N*-methyl-*o*-nitroaniline *p*-toluenesulfonanilide, 6892-25-7; sodium methanethiolate, 5188-07-8; γ-butyrolactone, 96-48-0.

(21) Preston, P. N. "Benzimidazoles"; Weissberger, A., Taylor, E. C., Eds.; John Wiley & Sons, Inc.: New York, 1981; Vol. 40, Part 1, pp 83–148.

(22) 5-Oxa-1-thiacyclooctane was prepared by cyclizing bis(4-bromopropyl) ether by an adaptation of the method of Singh, A.; Mehrotra, A.; Regen, S. L. *Synth. Commun.* **1981**, *11*, 409–411. The dichloro ether was prepared by the method of Sieber, G.; Ulbricht, I. *J. Prakt. Chem.* **1963**, *20*, 14–19. An improved procedure (50% vs. 10% yield) for the ten-membered ring, 6-oxa-1-thiacyclodecane, was realized by cyclizing bis-(4-iodobutyl) ether by a high-dilution adaptation of the method of Hammerschmidt, W.; Bieber, W.; Vögtle, F. *Chem. Ber.* **1978**, *111*, 2445–2447. The diiodide was obtained from the dichloride via a Finkelstein reaction. The dichloride was prepared by the method of Alexander, K.; Schniepp, L. E. *J. Am. Chem. Soc.* **1948**, *70*, 1839–1842.

Manganese(III)-Mediated γ-Lactone Annulation

William. E. Fristad* and John R. Peterson

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received November 14, 1983

The annulation of a γ-lactone ring onto an alkene by manganese(III) acetate oxidation of acetic acid was investigated. The regioselectivity of addition to unsymmetrically substituted alkenes is reported along with the stereoselectivity of addition to various acyclic and cyclic alkenes. Alkenes with ionization potentials above 8.2 eV were found to react in good yield. The role of acetic anhydride in these reactions was studied, and it was shown to be oxidized faster than acetic acid and also led to different products. The fate of oxidized acetic acid or anhydride in the absence of a suitable acceptor molecule has also been quantitatively identified. The relationship of enolizability, or C–H acidity, of the carboxylic acid being oxidized was established quantitatively.

Highly oxidized transition metals have long been used in organic synthesis (i.e., Cr(VI) in $H_2Cr_2O_7$ and Mn(VII) in $KMnO_4$) and their synthetic and mechanistic chemistry has been thoroughly studied.[1] Even so new uses are being discovered every year for these standard reagents.[2] Milder transition metal oxidants (i.e., Mn(III) species) have been far less commonly employed by synthetic chemists. Thus we have begun a program to exploit the synthetic potential

(1) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: Menlo Park, CA, 1972; pp 257–291.

(2) Lee, D. G.; Noureldin, N. A. *J. Am. Chem. Soc.* **1983**, *105*, 3188–3191.

0022-3263/85/1950-0010$01.50/0

Table I. Comparison of Lactonization by Hydrated and Anhydrous Manganese(III) Acetate

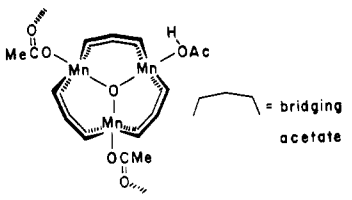
entry[a]	Mn(III) form	Mn(III),[b] equiv	lactone yield,[c] %
1	anhydrous	2.0	40
2	anhydrous	2.5	46
3	anhydrous	3.0	59
4	anhydrous	4.0	51
5	hydrate	2.0	62
6	hydrate	2.5	62
7	hydrate	3.0	77
8	hydrate	3.7	79
9	hydrate	4.5	88
10	hydrate	5.0	82

[a] A solution of 1-octene (0.1 M) was refluxed with manganese(III) acetate for 18–24 h at reflux. [b] Each manganese(III) acetate complex contains 3 equiv of Mn(III). [c] Yield was determined by GC integration with an internal standard and appropriate response factor.

of several unusual transition metal oxidant systems.

Anhydrous manganese(III) acetate, **1**, has been shown through an X-ray study to be an oxo-centered triangle of three manganese atoms held together by six bridging acetate ligands.[3] As such, a single manganese(III) acetate unit is capable of performing up to three sequential one-electron oxidations of a substrate while each Mn(III) is reduced to Mn(II). This interesting trinuclear structure is typical of transition metal(III) acetates,[4] and thus chemistry of **1** may illustrate general properties of many polynuclear metal oxidants. One might expect polynuclear metal oxidants to react in substantially different modes than mononuclear oxidants.

Manganese(III) acetate has been reported to produce γ-lactones by Bush and Finkbeiner[5] and Heiba et al.[6,7] These groups demonstrated the feasibility of the reaction and general reaction characteristics. In this report we wish to more carefully describe this annulation system. In particular, the role of acetic anhydride, the regio- and stereochemistry of annulation, and the limitations on reactive olefins will be delineated for the first time.



1

Table II. Lactonization with Manganese Hydrate in the Presence of Acetic Anhydride[a]

ratio HOAc/Ac_2O	Mn(III), equiv	reactn time,[b] h	lactone yield,[c] %
99:1	2.5	15	58
19:1	2.5	13.5	45
4:1	2.5	0.3	13
1:1	2.5	0.1	11
1:9	2.5	0.1	9

[a] A solution of 1-octene (0.1 M) was refluxed with manganese(III) acetate in the solvent combination described. [b] Reaction was considered complete when the dark brown reaction mixture turned completely colorless. [c] Yield was determined by GC integration with an internal standard and appropriate response factor.

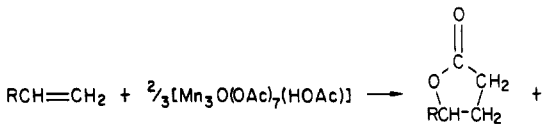
Table III. Lactonization with Manganese(III) Acetate in the Presence of Potassium Acetate[a]

[KOAc], M	Mn(III), equiv	reactn time, h	lactone yield,[c] %
0.005	2.5	23	67
0.010	2.5	>12[b]	78
0.10	2.5	>12[b]	65
0.20	2.5	>12[b]	65
0.50	2.0	7.5	85
3.05	2.0	1.3	81

[a] A solution of 1-octene or 1-decene (0.1 M) was refluxed with manganese(III) acetate and potassium acetate in acetic acid. [b] Time of manganese(III) decoloration was not noticed. Reaction was terminated at 24 h. [c] Yield was determined by GC integration with an internal standard and appropriate response factor.

Results

The stoichiometry of the γ-lactone annulation reaction is shown in eq 1. Two types of manganese(III) acetate



$2Mn(OAc)_2$ + HOAc (1)

are known, an anhydrous form[8] and a hydrate.[9] Both forms are easily prepared and may be stored indefinitely with no special precautions. We routinely make the cinnamon brown hydrate in 500-g quantities, althouth it is also commercially available.[10] The lactonization results with both species are summarized in Table I.

Previous reports[5,11] have indicated that the addition of acetic anhydride enhances the reaction rate (i.e., reduction of manganese(III)). We have corroborated this observation (Table II); however, the reaction products were dramatically altered! The addition of potassium acetate also enhanced the reaction rate; however, it now simultaneously increased the yield of lactone (Table III). These preliminary experiments led us to choose the following as optimum conditions for high lactone yield: olefin (0.1 M), manganese(III) acetate (0.083 M, 2.5 equiv of Mn(III)), and potassium acetate (0.5 M). The dark brown reaction

(3) Hessel, L. W.; Romers, C. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 545–552.

(4) Many other transition-metal oxo-centered acetates are known, i.e., V: Glowiak, T.; Kubiak, M.; Jesouska-Trzebiatowska, B. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1977**, *25*, 359. Cr: Chang, S. C.; Jeffrey, G. A. *Acta Crystallogr., Sect. B.* **1970**, *26B*, 673–683. Figgis, B. N.; Robertson, G. *Nature (London)* **1965**, *205*, 694. Fe: Auzumhofer, K.; DeBoer, J. J. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 286. Holt, E. M.; Holt, S. L.; Tucker, W. F.; Aspland, R. O.; Wabou, K. J. *J. Am. Chem. Soc.* **1974**, *96*, 2621–2623. Nb: Bino, A. *Ibid.* **1980**, *102*, 7990–7991. Mo: Bino, A.; Cotton, F. A.; Dori, Z. *Ibid.* **1981**, *103*, 243–244. Ru: Cotton, F. A.; Norman, J. G., Jr. *Inorg. Chim. Acta* **1972**, *6*, 411–419. Rh: Glowiak, T., Kubiak, M.; Szymanska-Buzar, T. *Acta Crystallogr., Sect. B* **1977**, *33B*, 1732–1737. W: Bino, A.; Cotton, F. A.; Dori, Z.; Koch, S.; Kuppers, H.; Millar, M.; Sekutowski, J. C. *Inorg. Chem.* **1978**, *17*, 3245–3253. Ir: Uemura, S.; Spencer, A.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1973**, 2565–2571. Harrison, B.; Logan, N. *Ibid.* **1972**, 1587–1589. Ciechanowicz, M.; Griffith, W. P.; Pauson, D.; Skapski, A. C.; Cleave, M. J. *J. Chem. Soc., Chem. Commun.* **1971**, 876.

(5) Bush, J. B., Jr.; Finkbeiner, H. *J. Am. Chem. Soc.* **1968**, *90*, 5903–5905.

(6) Heiba, E. I.; Dessau, R. M.; Koehl, W. J., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 5905–5906.

(7) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1974**, *96*, 7977–7981.

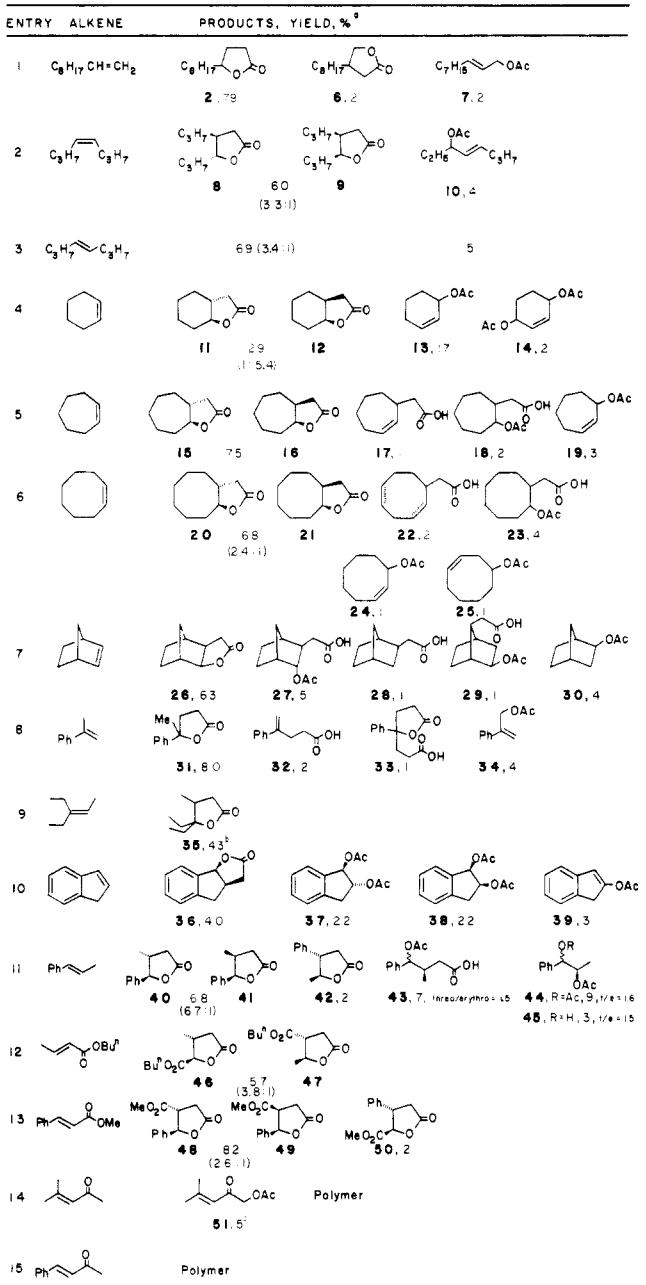
(8) Van Der Ploeg, R. E.; DeKorte, R. W., Kooyman, E. C. *J. Catal.* **1968**, *10*, 52–59.

(9) For numerous modifications of O. T. Christianson's procedure: *Z. Anorg. Allg. Chem.* **1901**, *27*, 321–328. See: Andrulis, P. J.; Dewar, M. J. S.; Dietz, R.; Hunt, R. L. *J. Am. Chem. Soc.* **1970**, *72*, 5473–5478. Finkbeiner, H. L.; Bush, J. B., Jr. German Patent 1 933 682; *Chem. Abstr.* **1970**, *72*, 89803. Gilmore, J. R.; Mellor, J. M. *J. Chem. Soc. C* **1971**, 2355–2357. Heiba, E. I.; Dessau, R. M.; Koehl, W. J., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 138–145. Brauer, G. "Handbook of Preparative Inorganic Chemistry", 2nd ed.; Academic Press: New York, 1965; Vol. 2, p 1469.

(10) Aldrich Chemical Co.

(11) Heiba, E. I.; Dessau, R. M.; Williams, A. L.; Rodewald, P. G. *Org. Synth.* **1983**, *61*, 22–24.

Table IV. General Lactonization Results



[a] Yields represent isolated products after chromatography and are based on reacted starting alkene. In all cases, except entries 4, 14, and 15, unreacted alkene amounted to less than 5% of the original alkene. [b] None of the regioisomer was observed. [c] Yield based on initial amount of mesityl oxide employed. Mesityl oxide was recovered in 31%.

mixture was refluxed until all the manganese(III) was reduced to the colorless manganese(II) acetate. These conditions were used to prepare the lactones listed in Table IV.

Discussion

General Data. The lactone annulations described previously by Bush and Finkbeiner[5] and Heiba et al.[6] based yields of lactone on the oxidant consumed and generally employed an excess of alkene. Our reaction conditions are a modification of the previous conditions in which now the lactone yield is maximized and based on the alkene.

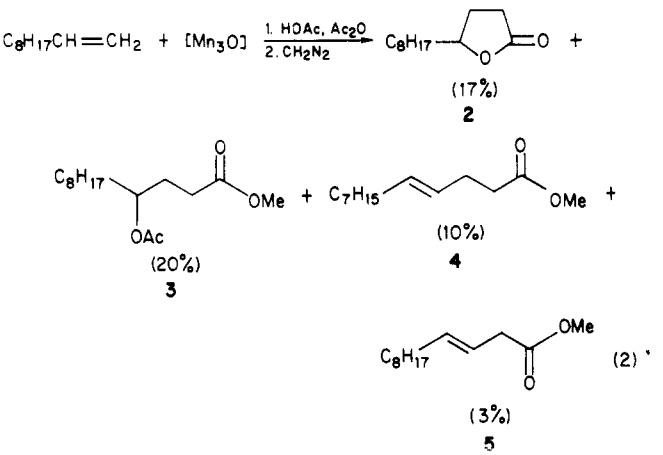
The comparison of hydrated and anhydrous manganese(III) acetate in Table I indicated that the hydrated form was much more efficient at lactone annulation. This

Table V. Oxidation in Mixed Acetic Acid/Acetic Anhydride Solvent Systems

solvent	yields, % 2	3	4 + 5
HOAc	79		
calcd amount of Ac_2O to consume H_2O	65	5	3
3.7-fold excess of Ac_2O to consume H_2O	17	33	10

may simply be the result of traces of acetic anhydride which remained in the anhydrous manganese(III) acetate, because as seen in Table II, the addition of acetic anhydride led to dramatic decreases in lactone yield. The acetic anhydride results were initially confusing to us since one earlier report had specifically employed large amounts of acetic anhydride (HOAc:Ac_2O, from 3:1 to 1:1) and claimed that it resulted in higher yields and shorter reaction times.[5] In contrast, other workers have found that reactions containing acetic anhydride produced a mixture of products.[12,13]

The results of several preparative scale reactions employing this mixed solvent system (HOAc:Ac_2O) are shown in eq 2 and summarized in Table V. It can be seen that



in the absence of acetic anhydride no γ-acetoxy acid **3** or unsaturated acids **4** or **5** were produced. When acetic anhydride was added to the reaction solvent in an amount equal to the water contained in the hydrated manganese(III) acetate, the yield of lactone dropped with the concomitant formation of **3**–**5**. An excess of acetic anhydride, indeed, led to the formation of **3** as the major product (33%). Lactone **2** was shown to be stable (100% recovery) when resubjected to the reaction conditions, and so **3** had to be produced directly in the Mn(III) reaction. Thus the addition of acetic anhydride to the lactonization system can cause very deleterious effects.

The previous workers had ascribed the rate accelerating effect of acetic anhydride to the removal of water of hydration which produced a more reactive anhydrous manganese(III) acetate. This explanation fails on several counts. First, as already shown, the products are different in the presence of excess acetic anhydride. Secondly, when the manganese(III) oxidation of acetic acid in the absence of olefin was conducted in the presence of 3-Å molecular sieves to remove the water of hydration, only a slight

(12) DeKlein, W. J. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 48–50, 151–153; German Patent 2 341 572; *Chem. Abstr.* **1974**, *80*, 145434. Akzo, N. V. Dutch Patent 7 210 545; *Chem. Abstr.* **1974**, *81*, 25094u.

(13) Okano, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1041–1046; *J. Sci. Hiroshima Univ., Ser. A: Phys. Chem.* **1976**, *40*, 169–193; *Chem. Ind. (London)* **1972**, 423.

Table VI. Relative Rates of Oxidation of Various Carboxylic Acids

acid	rel concn HOAc/acid	rel reactn time (t) t_{HOAc}/t_{acid}	reactn temp (T), °C	pK_a[a]	exptl rel rate, k/k_0[b]	calcd rel rate[c]
H–CH_2COOH	1	1	120	25	1	1
Cl–	2.18	5.2	120	22[d]	1.1×10^1	1.1×10^1
$PhSO_2$–	17.5	6.7	70	14	3.8×10^3	6.1×10^3
MeO_2C–	17.5	20	70	13	1.1×10^4	1.3×10^4
HO_2C–	17.5	25	70	13	1.4×10^4	1.3×10^4
NC–	43.7	20	65	9	4.0×10^5	3.2×10^5

[a] pK_a values of the corresponding esters in aqueous solution. [b] Experimental relative rate = (HOAc/acid)(t_{HOAc}/t_{acid})($2^{\Delta T/10}$). This assumes that the reaction rate will double for each 10 °C temperature increase. [c] Calculated from the graphically derived equation; log (rel rate) = 0.344(ΔpK_a). [d] Reutov, O. A.; Beletskaya, I. P.; Butin, K. P. "CH-Acids"; Pergamon Press: Oxford, 1978; p 61.

(1.7-fold) rate enhancement was observed. The rate increase in the presence of acetic anhydride was 15-fold over the rate of manganese(III) reduction in glacial acetic acid. Thus the course of the reaction is completely different in the presence of acetic anhydride but relatively is unaffected by small amounts of water in acetic acid.

A more reasonable accounting for the difference in reaction course between acetic anhydride containing reactions and those not is that acetic anhydride is simply oxidized much faster than acetic acid. Other work in our laboratory has shown that the rate of oxidation increases with increasing enolizability, or acidity of an α-proton, of the carbonyl compound being oxidized.[14,15] Thus the reaction rate follows the C–H acidity order. In an attempt to quantify the relationship of reaction rates and C–H acidity, a series of six carboxylic acids has been compared (Table VI). Oxidation of all these acids gave rise to lactone products which ensured that a similar oxidation mechanism was involved in every case. The relative reactivity of each acid in question was calculated from the concentration of the acid relative to the acetic acid solvent, the reaction time for all the manganese(III) to be reduced for acetic acid and the acid in question, and a simplistic temperature correction. Experimentally the acids span a relative reactivity of over 10^5, which does allow very specific reactions to take place. When the log (relative reactivity) was plotted against the difference in C–H pK_a values of the corresponding esters in a typical linear free energy plot, a straight line with a slope of 0.344 was obtained (Figure 1). This correlation demonstrates the important relationship of reaction rate with the enolizability, or C–H acidity, of the complexed carboxylate ligand.

Acetic anhydride cannot be compared directly on the same scale because it has no free carboxylate to ligate to the manganese(III) complex. The experimental relative reaction rate in the presence of olefin, however, still shows an enhancement over acetic acid by a factor of 30. The calculated relative reactivity (estimating an aqueous pK_a of 18) for acetic anhydride would be approximately 250. Thus the increased C–H acidity of acetic anhydride does make it more reactive than acetic acid. In this regard, the rate and yield enhancement noticed with increased concentration of potassium acetate (see Table III) suggest that acetate is acting as a base to effect deprotonation. This conclusion is consistent with previous work which showed the rate enhancing effect of electron-withdrawing groups on substituted ketone oxidation by Mn(III).[16]

Finally, we have shown that the oxidation of acetic anhydride and acetic acid give different products in the absence of olefin. In all the previous work with manganese(III) acetate oxidations, the oxidation products in the absence of olefin or other unsaturated acceptor molecule have not been quantitatively identified.[8,13] When manganese(III) acetate was reduced to manganese(II) acetate in pure acetic acid, the organic products obtained were carbon dioxide (100%), succinic acid (<1%), and acetoxyacetic acid (<1%). The carbon dioxide was determined as barium carbonate, the organic acids were determined by ^{1}H NMR, and the yields were determined on the basis of Mn(III) consumed. In contrast, when manganese(III) acetate was reduced in an acetic acid/acetic anhydride mixture (1:19), the products were carbon dioxide (39%), succinic acid anhydride (52%), and acetoxyacetic anhydride (9%). Once again the fates of oxidized acetic acid and acetic anhydride were quite different.

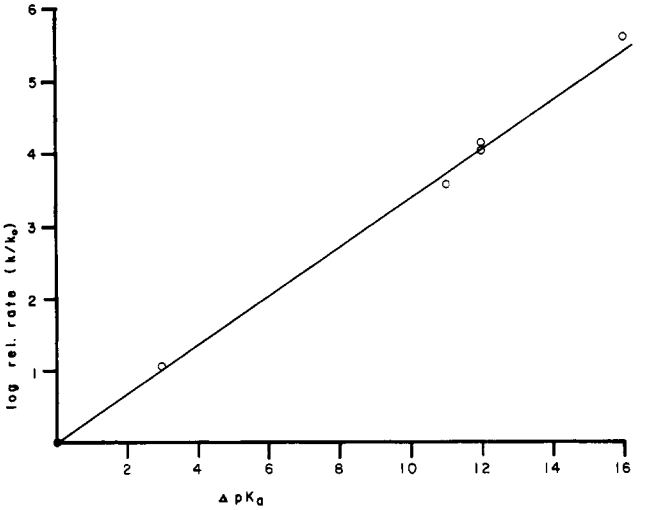


Figure 1. Hammett plot of the log (relative rate) of oxidation of the substituted acetic acids X–CH_2CO_2H vs. the difference in pK_a units between acetic and the substituted acid: correlation coefficient = 0.999; slope = 0.344.

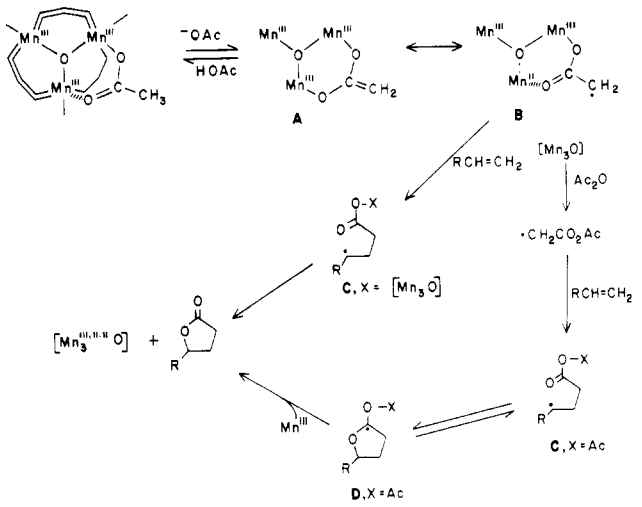
We propose the sequence of intermediate oxidation states in eq 3 for acetic acid oxidation. This was corrob-

$$CH_3COOH \xrightarrow{2Mn(III)} AcOCH_2COOH \xrightarrow{2Mn(III)} (AcO)_2CHCOOH \xrightarrow{2Mn(III)} HOOCCOOH \xrightarrow{2Mn(III)} 2CO_2 \quad (3)$$

orated by the separate conversion to carbon dioxide of acetoxyacetic acid (96%) and oxalic acid (96%). In the latter case the oxidation was instantaneous, which explained its absence among the final oxidation products. The net formation of only CO_2 when oxidized acetic acid is not trapped by an olefin explains the cleanliness of the present Mn(III) lactonization sequence. Acetic anhydride gave a substantial amount of the C–C coupling product. The important difference to note is that acetic acid gave no C–C coupling products which implies no substantial amount of free acetic acid radicals (·CH_2COOH) as proposed by Heiba whereas acetic anhydride did lead to substantial coupling, presumbably via free radicals of the type ·$CH_2CO_2COCH_3$.[17] The unmistakable conclusion of

(14) Peterson, J. R.; Hershberger, S. S., unpublished results.
(15) Enolization increases with electron-withdrawing groups X in CH_3COX: Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Wiley-Interscience: New York, 1975; p 278.
(16) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* 1971, *93*, 524–527.

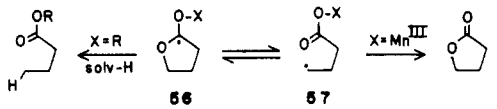
Scheme I



these experiments is that acetic anhydride is oxidized in preference to acetic acid and that the reaction products can be very different.

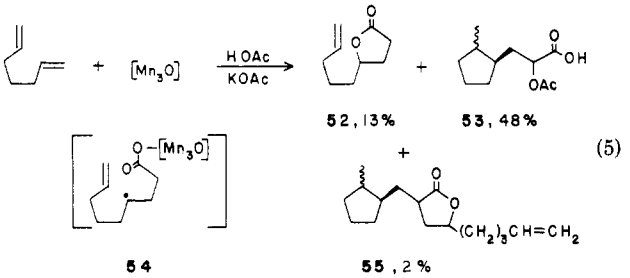
The results in Table IV show that in addition to the γ-lactones, lesser amounts of other products were obtained. The minor products were of two general types: allylic acetates and unsaturated or γ-acetoxyacids. These and the previous results[5,6] are consistent with the mechanism proposed in Scheme I. The allylic acetates could be produced by allylic hydrogen abstraction by a radical intermediate or the complexed radical B, followed by a ligand transfer oxidation. The γ-acetoxy acids could be formed by a similar ligand transfer oxidation via C, and the unsaturated acids could result from single electron transfer oxidation of C with loss of a proton.

Further evidence for the short-lived radical intermediate C was the result of lactone annulation with 1,6-heptadiene (eq 4). The proposed intermediate radical **54** would be



(4)

expected to cyclize rapidly either via the alkene to eventually give **53** or via the carbonyl to give **52**. Compound **53** can be envisioned being formed by cyclization of radical **54** to a methylcyclopentyl radical that undergoes 1,5 H transfer to generate the more stable α-carboxy radical. This radical could then be oxidized to the acetoxy acid by a ligand transfer oxidation in the same manner as **3**. Radical **54** should cyclize to **53** at a rate comparable to the 6-hepten-2-yl radical which is known to cyclize to the (2-methylcyclopentyl)methyl radical with $k = 1.3 \times 10^5$ s^{-1} (25 °C).[18,19] An actual rate constant for cyclization of a radical γ to the carbonyl group of an acid or ester is not available; however, this radical is known to cyclize rapidly in the presence of a copper(II) oxidant.[20] Thus a radical of type **57**, X = H or Mn(III), has been converted to the lactone in the presence of an oxidant, while in the absence of an oxidant either **57** or **56** was converted only to the open chain ester (eq 5).[21]



(5)

Heiba and Dessau reported that 1,6-heptadiene under their Mn(III) lactonization conditions had cyclized to give 3-(3-acetoxycyclohexyl)propionic acid as the major product, although no yield or physical data were reported.[7] We found no evidence for six-membered ring containing products. Their conclusion that cyclization to a lactone occurred through a carbocation is not consistent with our results; however, cyclization via a radical seems more probable.

The next mechanistic question is what is the fate of the radical C (Scheme I)? Heiba and Dessau proposed oxidation of the radical to the cation, followed by cyclization to the lactone with loss of a proton.[6,7] The intermediacy of cations in the lactonization mechanism would not be consistent with the result of norbornene (entry 7, Table IV). No rearranged lactone products were obtained, and the corresponding 2-norbornyl cation after acetic acid addition has been made by different means and shown by Davies and Dowle to give the rearranged δ-lactone under kinetic conditions.[22] Only under prolonged acidic isomerization conditions was the δ-lactone converted to the γ-lactone **26**. The only product resulting from rearrangement was 2-*exo*-acetoxy-7-*syn*-bicyclo[2.2.1]heptane acetic acid, **29**, in 1%.[23] We therefore favor the direct conversion of an intermediate C to the lactone with no intervention of carbocations.

Oxidation of acetic anhydride by manganese(III) acetate can also be interpreted by using a mechanism similar to that of acetic acid oxidation in Scheme I. However very importantly when acetic anhydride is oxidized, a complexed radical analogous to B cannot be formed, and instead a free radical eventually leading to C, X = Ac, would be produced. This radical can suffer two fates depending on R. In our experiment (eq 3), R = octyl, cyclization of C → D, X = Ac, and subsequent oxidation to a lactone are not the dominant pathway. Rather the γ-acetoxyacid is produced. In Bush and Finkbeiner's experiment,[5] R = phenyl, the benzylic radical in C, X = Ac, may be oxidized to a carbocation via a single electron transfer which then cyclized to the γ-lactone. Thus when R can greatly stabilize an adjacent carbonium ion, lactones could still be produced by acetic anhydride oxidation. However when R does not greatly stabilize a carbocation, γ-acetoxy acids and not lactones become the predominant product.

Regiochemistry. Before this manganese-mediated lactone annulation can be utilized fully in synthetic organic applications, the regio- and stereochemical consequences must be known. No regioselectivities have been reported

(17) A 50% yield of succinic acid was obtained when free carboxymethyl radicals, $\cdot CH_2COOH$, were generated from decomposition of diacetyl peroxide. Fry, A.; Tolbert, B. M.; Calvin, M. *Trans. Faraday Soc.* **1953**, *49*, 1444–1451.

(18) Maeda, Y.; Ingold, K. U. *J. Am. Chem. Soc.* **1979**, *101*, 4975–4981.

(19) The 6-hepten-2-yl radical generally results in a cis:trans dimethylcyclopentane ratio of 2–3:1. Rilatt, J. A.; Kitching, W. *Organometallics* **1982**, *1*, 1089–1093.

(20) Citterio, A.; Arnoldi, A.; Minisci, F. *J. Org. Chem.* **1979**, *44*, 2674–2682.

(21) Rynard, C. M.; Thankachen, C.; Tidwell, T. T. *J. Am. Chem. Soc.* **1979**, *101*, 1196–1201. Huyser, E. S. *J. Org. Chem.* **1960**, *25*, 1860.

(22) Davies, D. I.; Dowle, M. D. *J. Chem. Soc., Perkin Trans 1* **1978**, 227–231.

(23) 2-Norbornyl radical, unlike the corresponding cation, does not undergo rapid rearrangement: Whitesides, G. M.; San Filippo, J., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 6611–6624. Davies, D. I.; Cristol, S. J. *Adv. Free-Radical Chem.* **1965**, *1*, 155–209.

Table VII. Thermodynamic Stability of Lactones

compd	isomerized ratio trans:cis	Mn lactonizatn ratio trans:cis
8	8.7:1	3.3:1
9	8.7:1	
11	1:3.8	1:5.4
12	1:3.8	
15	1.1:1	1:1.4
16	1.1:1	
20	*a*	2.4:1
21	*a*	

[a] Sample was decomposed by the isomerization conditions.

aside from identifying the major product, and in at least one case the stereoselectivity was incorrectly assigned. The regiochemistry of lactone annulation is easily predicted and generally high. A terminal alkene (entry 1, Table IV) reacted with a regioselectivity of 40:1, which showed the preference of a secondary over a primary radical intermediate. Entry 9 indicated the tertiary/secondary selectivity was >60:1. Entries 11 and 8 showed a benzylic/secondary selectivity of >38:1 and tertiary benzylic/primary selectivity of >160:1. A benzylic radical intermediate was favored over a radical α to an ester, entry 13 by 41:1, while the regiochemistry was reversed when the benzylic center was replaced by a secondary, entry 12, 3.8:1.

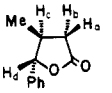
Stereochemistry. The stereoselectivity of lactone annulation is not so pronounced and is highly dependent on the nature of the alkene utilized. Acyclic alkenes gave the trans-substituted lactones with a stereoselectivity ranging from 3.3:1 (entry 2) to 67:1 (entry 11). Generation of essentially the same trans/cis lactone mixture from both *trans*- and *cis*-4-octene (entries 2 and 3) indicated that the lactone annulation was not a concerted process and that rotational equilibration of the reactive intermediate occurs. The stereoselection of annulation onto cyclic alkenes was less easily predicted; however, it followed a smooth progression. Annulation onto a cyclopentene moiety (entry 10) of course produced only the cis-fused lactone. Cyclohexene, cycloheptene, and cyclooctene showed a regular progression toward more trans-fused lactones (entries 4–6). The trans/cis ratios that were obtained apparently reflect the transition-state energies of cyclization rather than strictly the thermodynamic stability of the isomeric lactones. When the individual isomeric lactones were equilibrated under acidic conditions[24] (50% aqueous H_2SO_4/HOAc, reflux), a similar but not identical ratio of lactones was obtained (Table VII). It should be noted that the thermodynamic stability of these ring-annulated lactones differ substantially from their all-carbon bicyclic counterparts.[25,26]

The present manganese(III) acetate lactone annulation procedure works efficiently for most alkenes. As observed in entries 10 and 11, however, formation of 1,2-diacetates and 1,2-hydroxyacetates can occur in rather electron-rich alkenes. Other work in this laboratory has shown that the lower ionization potential cutoff for useful alkenes in the lactonization process is 8.2 eV.[27] Below this level other oxidations ensue.

Structure Assignments. Assignment of substituent stereochemistry on a γ-lactone moiety by NMR coupling constant data is difficult. Generally $J_{trans} > J_{cis}$ for vicinal ring hydrogens;[28] however, this is not always the case.[29] We have identified the stereochemistry of lactones 8 and 40 by an independent synthesis and a difference NOE experiment, respectively (see Experimental Section). In addition, the NMR spectra of several other lactones matched that of literature compounds. A comparison of the chemical shift values for the C*H*OC(=O) hydrogen of all the lactones which were produced as trans/cis mixtures are shown in Table VIII. In all cases the signal of the trans-substituted lactone resonates at higher field than the cis isomer. This can be explained by shielding of this hydrogen by the adjacent C–C bond.[30] This observation is also consistent with other lactone pairs in the literature[28,29] and appears to be a useful diagnostic feature.

Table VIII. Comparison of >C*H*OC(=O) Chemical Shift Values for Trans and Cis Lactones

alkene, lactones	δ, trans	δ, cis	Δδ
4-octene, **8**, **9**	4.05	4.45	0.40
cyclohexene, **11**, **12**	3.75	4.52	0.77
cycloheptene, **15**, **16**	4.15	4.65	0.50
cyclooctene, **20**, **21**	4.37	4.60	0.27
norbornene, **26**		4.43	
β-methylstyrene, **40**, **41**	4.91	5.55	0.64
methyl cinnamate, **48**, **49**	5.64	5.75	0.11



40

Conclusion

The manganese(III) acetate lactone annulation procedure is a simple, one-pot method for preparing γ-lactones of predictable regio- and stereochemistry. Isolated yields are generally 60–80%. This compares favorably with other multistep routes to lactone annulation and in certain cases produces the opposite regio- or stereochemical isomer. The synthetic utility of this reaction has been demonstrated, and further mechanistic studies are still in progress.

The effect of acetic anhydride on these oxidations has been explained and is a result of it being oxidized itself. The fate of the oxidized acetic acid or anhydride in the absence of a suitable acceptor molecule has been identified. The linear relationship between the log of the relative reactivity of substituted acetic acids and their C–H acidity (pK_a of the corresponding ester) demonstrated the importance of substrate acidity in this reaction.

Experimental Section

Melting points were determined with an Electrothermal apparatus and are uncorrected. ^1H NMR spectra were obtained on a Varian HFT-80 (80-MHz) or a Nicolet 300-MHz instrument. Chemical shifts are reported in parts per million relative to internal $(CH_3)_4Si$ in $CDCl_3$ unless specified otherwise. Mass spectra were obtained with an AE1 Kratos MS-30 (electron impact) or a Finnigan 4000 (chemical ionization) spectrometer. Infrared spectra were obtained on a Beckman 4250 spectrophotometer. Gas chromatography was performed with a Varian 3700 Model

(24) Klein, J. *J. Am. Chem. Soc.* **1959**, *81*, 3611–3614.
(25) Laali, K.; Muller, M.; Sommer, J. *J. Chem. Soc., Chem. Commun.* **1980**, 1088–1089.
(26) Chang, S.; McNally, D.; Shary-Tehrany, S.; Hickey, Sister M. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109–3118.
(27) The 1,2-diacetates were produced by single electron transfer oxidation of low IP alkenes which was followed by solvent capture rather than ligand oxidation which produced the lactone. Fristad, W. E.; Peterson, J. R.; Ernst, A. B., manuscript in preparation.
(28) Mandel'shtam, T. V.; Kolesova, S. V.; Polina, T. V.; Solomentsev, V. V.; Osmolovskaya, N. S. *J. Org. Chem. USSR (Engl. Transl.* **1980**, *16*, 1024–1031. Bystrom, S.; Hogberg, H. E.; Norin, T. *Tetrahedron* **1981**, *37*, 2249–2254.
(29) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; Van Derveer, D. *J. Org. Chem.* **1980**, *45*, 3846–3856. Padwa, A.; Brookhardt, T.; Dehm, D.; Wubbels, G. *J. Am. Chem. Soc.* **1978**, *100*, 8247–8259.
(30) Silverstein, R. M., Bassler, G. C.; Morrill, T. C. "Spectrometric Identification of Organic Compounds", 4th ed., Wiley: New York, 1981; p 189.

equipped with FID's and a Hewlett-Packard 3390A integrator. The columns used were 5% Carbowax 20M on 100/120 mesh Chromosorb W, 0.3 cm × 6 m, 10% SF-96 on 80/100 mesh Chromosorb W, 0.3 cm × 6 m, or a silver nitrate/ethylene glycol on 80/100 mesh Chromosorb P to determine alkenes and lactones. Products were isolated by medium-pressure liquid chromatography (FMI pump, silica gel column, refractive index detector, Altex Model 156).

Starting alkenes were commercially obtained except *cis*-4-octene which was prepared by a literature method[31] and found to be 97% *cis*-4-octene contaminated by 3% of the trans isomer. Manganese(III) acetate was prepared by literature methods.[8,9] References after a compound name refer to literature spectral data that matched the present results.

General Procedure for Lactone Yield Optimization. A 25-mL round-bottom flask equipped with a reflux condensor, magnetic stirrer, and a nitrogen inlet was charged with the alkene indicated (1 mmol), the manganese(III) acetate form indicated, potassium acetate if specified, and the indicated solvent system. The mixture was brought to reflux which resulted in a dark brown solution. Upon turning colorless, the reaction mixture was cooled, diluted with water (3–4 × volume), and extracted with 30–60 °C petroleum ether or ether (3 × 10 mL). The combined extracts were washed with water (2 × 8 mL) and saturated sodium bicarbonate (2 × 8 mL), dried ($MgSO_4$), and analyzed by gas chromatography. Decane or dodecane were used as internal standards.

Preparation of Dihydro-5-octyl-2(3*H*)-furanone (2)[32] in the Presence of Acetic Anhydride. 1-Decene (7.0 mmol), manganese(III) acetate hydrate (4.67 mmol), acetic anhydride (17.5 mL), and glacial acetic acid (52.5 mL) were refluxed under nitrogen until the brown solution turned colorless (1.5 h). The reaction mixture was cooled, diluted with water (300 mL), and extracted with ether (5 × 50 mL). The combined ether extracts were washed with water (5 × 50 mL), dried ($MgSO_4$), and concentrated. The crude product was treated with an excess of diazomethane in ether, dried ($MgSO_4$), and evaporated. Chromatography (EtOAc:hexane, 1:4) yielded **2** (0.240 g, 1.21 mmol, 17%), **3**, and a mixture of anhydrides. The anhydrides were hydrolyzed with refluxing 6 N HCl and reesterified. Chromatography of this material gave more **3** (a total of 0.38 g, 1.40 mmol, 20%) and a mixture of methyl (*E*)-4-dodecenoate, **4**, and methyl (*E*)-3-dodecenoate, **5** (0.184 g, 0.87 mmol, 13%, as a 78:22 mixture by GC).

2: IR 2920, 2850, 1775, 1460, 1350, 1175, 1010, 975, 910 cm^{-1}; NMR δ 4.45 (m, 1 H), 2.70–0.60 (m, 21 H); exact mass calcd for $C_{12}H_{22}O_2$ $(m + 1)/z$ 199.1692, found 199.1685, calcd m/z 198.1614, found 198.1614.

3: IR 2925, 2855, 1740, 1435, 1370, 1235, 1170, 1020 cm^{-1}; NMR δ 4.85 (m, 1 H), 3.67 (s, 3 H), 2.23 (m, 2 H), 2.03 (s, 3 H), 1.85–0.70 (m, 19 H); exact mass calcd for $C_{15}H_{28}O_4$ $(m - Ac)/z$ 229.1787, found 229.1797.

4 and 5: IR 2925, 2855, 1740, 1435, 1250, 1190, 1160, 960 cm^{-1}; NMR δ 5.60–5.10 (m, 2 H), 3.66 (s, 3 H), 2.50–0.50 (m, 19 H); exact mass calcd for $C_{13}H_{24}O_2$ m/z 212.1783, found 212.1770.

Lactone Annulation onto 1,6-Heptadiene. The general lactonization procedure below followed by diazomethane esterification of the crude acidic product mixture yielded after chromatography (EtOAc/hexane, 3:17) **52** (13%), **53**-methyl ester (48%), and **55** (2%).

52: IR 3075, 2940, 2860, 1775, 1640, 1455, 1235, 1175, 910 cm^{-1}; NMR δ 6.00–5.45 (m, 1 H), 5.15 (br d, 1 H, J = 7 Hz), 4.83 (br s, 1 H), 4.42 (br quint, 1 H, J = 6 Hz), 4.61–4.2 (m, 1 H), 2.7–1.2 (m, 10 H); exact mass calcd for $C_9H_{14}O_2$ $(m + 1)/z$ 155.1068, found 155.1071, calcd m/z 154.0990, found 154.0997.

53-Me ester (mixture of diastereomers): IR 2950, 2870, 1745, 1475, 1375, 1225, 1170, 1055, 915 cm^{-1}; NMR δ 5.10–4.85 (m, 1 H), 3.74 (s, 3 H), 2.13 (s, 3 H), 2.50–0.70 (m, 10 H), 0.85 (d, 3 H, J = 7 Hz); exact mass calcd for $C_{12}H_{20}O_4$ $(m + 1)/z$ 229.1446, found 229.1426, calcd m/z 228.1356, found 228.1368.

55 (mixture of diastereomers): IR 3075, 2950, 2870, 1770, 1640, 1455, 1370, 1235, 1170, 1020 cm^{-1}; NMR δ 6.00–5.45 (m, 1 H), 5.15–4.80 (m, 2 H), 4.65–4.35 (m, 1 H), 2.70–0.70 (m, 22 H); exact mass calcd for $C_{16}H_{28}O_2$ $(m + 1)/z$ 251.2004, found 251.2018, calcd m/z 250.1926, found 250.1954.

Table IX. NOE Experiment with 40

hydrogen irradiated	effected hydrogen	rel magnitude of NOE corrected for no. of protons
CH_3	H_b	3.6
	H_c	4.3
	H_d	8.6
	Ph	1.0
H_c	H_a	
	H_b	1.4
	Me	1.0
H_d	H_c	
	Me	large

Independent Synthesis of *trans*-Dihydro-4,5-dipropyl-2-(3*H*)-furanone (8). Addition of dichloroketene to *trans*-4-octene by the method of Hassner[33-35] produced *trans*-2,2-dichloro-3,4-dipropylcyclobutanone, **58**, which was reduced to *trans*-1,2-dipropylcyclobutanone, **59**, with zinc in acetic acid. Baeyer–Villiger oxidation of **59** resulted in γ-lactone **8** being produced in 26% overall yield. The material consisted of exclusively one isomeric lactone that was identical with **8** produced via manganese(III) acetate lactonization by spectral and GC comparison.

58: IR 2960, 2930, 2880, 1805, 1465 cm^{-1}; NMR δ 3.14 (dt, 1 H, J = 10, 7 Hz), 2.51 (dt, 1 H, J = 10, 7 Hz), 2.0–1.1 (m, 8 H), 1.00 (t, 6 H, J = 7 Hz).

59: IR 2960, 2930, 2880, 1780, 1465, 1225 cm^{-1} NMR δ 3.2 (m, 4 H), 2.0–1.1 (m, 8 H), 0.95 (m, 6 H).

Difference Nuclear Overhauser Enhancement (NOE) Experiment with *trans*-Dihydro-4-methyl-5-phenyl-2-(3*H*)-furanone (40). Hydrogens H_a–H_d were assigned from the 300-MHz NMR [δ 7.34 (m, 5 H, aromatic), 4.91 (d, 1 H, J = 8.29 Hz, H_d), 2.76 (dd, 1 H, J = 16.56, 7.42 Hz, H_b), 2.56–2.38 (m, 1 H, H_c), 2.32 (dd, 1 H, J = 16.56, 10.47 Hz, H_a), 1.42 (d, 3 H, J = 6.10 Hz, CH_3)] and the NOE study (Table IX) and were consistent with anticipated coupling constants from a Drieding model. Table IX shows strong NOE effects between Me–H_d, H_c–H_b, and H_d–Me and correspondingly small or negligible effects between H_d–H_c and H_c–H_a. Thus a cis relationship is indicated between H_b–H_c and Me–H_d.

General Synthetic Procedure for Lactone Annulation with Manganese(III) Acetate. A 100-mL round-bottom flask equipped with a reflux condenser, nitrogen inlet, and a magnetic stirrer was charged with the alkene (5.00 mmol), hydrated manganese(III) acetate (4.17 mmol), potassium acetate (25 mmol), and glacial acetic acid (50 mL). The mixture was refluxed until the dark brown color disappeared, cooled, and diluted with water (200 mL). The organic products were extracted with ether (5 × 40 mL). The combined ether extracts were washed with water (2 × 40 mL), saturated sodium bicarbonate (2 × 40 mL), dried ($MgSO_4$), evaporated, and chromatographed.

The sodium bicarbonate washes were acidified with 6 N HCl and extracted with ether (3 × 25 mL). The ether extracts were combined, washed with water (3 × 25 mL), dried ($MgSO_4$), evaporated, and esterified by ethereal diazomethane. The esters were purified by chromatography.

Structural Data for Compounds in Table IV. Dihydro-4-octyl-2(3*H*)-furanone (6): IR 2925, 2850, 1780, 1465, 1370, 1220, 1165, 1020 cm^{-1}; NMR δ 4.38 (dd, 1 H, J = 9, 7 Hz), 3.86 (dd, 1 H, J = 9, 8 Hz), 2.80–1.9 (m, 3 H), 1.7–0.6 (m, 17 H); exact mass calcd for $C_{12}H_{22}O_2$ $(m + 1)/z$ 199.1692, found 199.1672, calcd m/z 198.1614, found 198.1626.

(*E*)-2-Decenol acetate (7):[36] IR 3020, 2955, 2980, 2850, 1738, 1460, 1370, 1230, 1020, 965 cm^{-1}; NMR δ 5.60 (m, 2 H), 4.45 (d, 2 H, J = 6 Hz), 2.05 (s, 3 H), 2.55–0.70 (m, 15 H); exact mass calcd for $C_{12}H_{22}O_2$ m/z 198.1614, found 198.1626.

***trans*-Dihydro-4,5-dipropyl-2(3*H*)-furanone (8)**: IR 2960,

(31) Brown, H. C.; Brown, C. A. *J. Am. Chem. Soc.* **1963**, *85*, 1005–1006.

(32) Sucrow, W.; Klein, U. *Chem. Ber.* **1975**, *108*, 3518–3521.

(33) Brady, W. T.; Liddell, H. G.; Vaughn, W. C. *J. Org. Chem.* **1966**, *31*, 626–627.

(34) Hassner, A.; Fletcher, V. R.; Hamon, D. P. G. *J. Am. Chem. Soc.* **1971**, *93*, 264–265.

(35) Vedejs, E.; Dolphin, J. M.; Mastalerz, H. *J. Am. Chem. Soc.* **1983**, *105*, 127–130.

(36) Compared to (*E*)-2-hexenol acetate.

2930, 2870, 1770, 1465, 1170, 1000, 960 cm^{-1}; NMR δ 4.05 (br q, 1 H, J = 7 Hz), 2.85–1.9 (m, 3 H), 1.9–1.0 (m, 8 H), 1.0–0.7 (m, 6 H); exact mass calcd for $C_{10}H_{18}O_2$ $(m + 1)/z$ 171.1380, found 171.1378, calcd m/z 170.1302, found 170.1309.

***cis*-Dihydro-4,5-dipropyl-2(3*H*)-furanone (9)**: IR 2960, 2930, 2870, 1770, 1465, 1170, 1000, 960 cm^{-1}; NMR δ 4.43 (m, 1 H), 2.75–2.0 (m, 3 H), 1.9–1.5 (m, 8 H), 1.1–0.7 (m, 6 H); exact mass calcd for $C_{10}H_{18}O_2$ (m/z) 170.1302, found 170.1303.

(*E*)-4-Octen-3-ol acetate (10):[37] IR 2960, 2930, 2870, 1735, 1670, 1465, 1370, 1240, 1020, 965 cm^{-1}; NMR δ 5.90–5.00 (m, 3 H), 2.03 (s, 3 H), 2.40–1.8 (m, 2 H), 1.8–1.1 (m, 4 H), 1.1–0.7 (m, 6 H).

***trans*-Hexahydro-2(3*H*)-benzofuranone (11)**:[38] IR 2940, 2860, 1780, 1210, 1185, 1075, 1030, 930 cm^{-1}; NMR δ 3.75 (br td, 1 H, J = 10, 4 Hz), 2.7–2.1 (m, 3 H), 2.1–1.0 (m, 8 H); exact mass calcd for $C_8H_{12}O_2$ $(m + 1)/z$ 141.0912, found 141.0911, calcd m/z 140.0834, found 140.0834.

***cis*-Hexahydro-2(3*H*)-benzofuranone (12)**:[38] IR 2930, 2855, 1785, 1450, 1425, 1225, 1180, 1140, 990, 947, 940, 730, 690 cm^{-1}; NMR δ 4.52 (m, 1 H), 2.90–0.95 (m, 11 H); exact mass calcd for $C_8H_{12}O_2$ m/z 140.0834, found 140.0833.

2-Cyclohexenol acetate (13):[39] IR 3075, 2940, 2870, 2840, 1730, 1650, 1440, 1370, 1235, 1030, 1010, 905, 725 cm^{-1}; NMR δ 5.90 (br dt, 1 H, J = 10, 3 Hz), 5.62 (br d, 1 H, J = 10 Hz), 5.25 (br q, 1 H, J = 4 Hz), 2.04 (s, 3 H), 2.60–1.20 (m, 6 H); exact mass calcd for $C_8H_{12}O_2$ m/z 140.0834, found 140.0839.

2-Cyclohexene-1,4-diol diacetate (14):[40] IR 3040, 2940, 2870, 1735, 1370, 1230, 1030, 915 cm^{-1}; NMR δ 5.89 (d, 2 H, J = 1.2 Hz), 5.5–5.2 (m, 2 H), 2.05 (s, 6 H), 2.3–1.6 (m, 4 H); CI-MS (NH_3 ionization gas) for $C_{10}H_{14}O$ (positive) $(m + NH_4^+)/z$ 216, found 216, (negative) calcd $(m - 1)/z$ = 197, found 197.

***trans*-Octahydro-2*H*-cyclohepta[*b*]furan-2-one (15)**:[38] IR 2925, 2860, 1775, 1450, 1180, 1000 cm^{-1}; NMR δ 4.15 (m, 1 H), 2.90–1.05 (m, 13 H with peaks at 2.42, 2.30, 2.17, and 2.02); exact mass calcd for $C_9H_{14}O_2$ m/z 154.0990, found 154.0993.

***cis*-Octahydro-2*H*-cyclohepta[*b*]furan-2-one (16)**:[38] IR 2920, 2855, 1775, 1455, 1360, 1170, 1010 cm^{-1}; NMR δ 4.65 (ddd, 1 H, J = 10.5, 7.5, 4.5 Hz), 3.00–0.85 (m, 13 H, with peaks at 2.85–2.27 and 2.17); exact mass calcd for $C_9H_{14}O_2$ m/z 154.0990, found 154.0988.

Methyl 2-cycloheptenylacetate (17-Me ester): IR 3015, 2920, 2855, 1740, 1205 cm^{-1}; NMR δ 5.65 (m, 2 H), 3.67 (s, 3 H), 2.50–1.05 (m, 11 H).

Methyl 2-acetoxycycloheptylacetate (18-Me ester; 3:2 isomer mixture): IR 2925, 2855, 1735, 1435, 1370, 1245, 1020 cm^{-1}; NMR δ 4.95 (m, 0.4 H), 4.60 (m, 0.6 H), 3.67 (s, 3 H), 2.02 (s, 3 H), 2.50–1.10 (m, 13 H); exact mass calcd for $C_{12}H_{20}O_4$ $(m - Ac)/z$ 185.1173, found 185.1177.

2-Cycloheptenol acetate (19): IR 3030, 2925, 2855, 1730, 1440, 1370 d, 1240, 1020 cm^{-1}; NMR δ 6.05–5.15 (m, 3 H), 2.05 (s, 3 H), 2.50–1.10 (m, 8 H); exact mass calcd for $C_9H_{14}O_2$ m/z 154.0990, found 154.0988.

***trans*-Octahydrocycloocta[*b*]furan-2(3*H*)-one (20)**:[41] IR 2930, 2850, 1775, 1468, 1450, 1315, 1205, 1110 cm^{-1}; NMR δ 4.37 (m, 1 H), 2.90–0.80 (m, 15 H); exact mass calcd for $C_{10}H_{16}O_2$ m/z 168.1146, found 168.1141.

***cis*-Octahydrocycloocta[*b*]furan-2(3*H*)-one (21)**: IR 2920, 2850, 1785, 1470, 1450, 1345, 1180, 1020, 990, 962 cm^{-1}; NMR δ 4.60 (1 H, J = 7 Hz), 2.90–0.90 (m, 15 H); exact mass calcd for $C_{10}H_{16}O_2$ m/z 168.1146, found 168.1141.

Mixture of methyl 2- and 4-cyclooctenylacetates (22):[42] IR 3015, 2925, 2850, 1740, 1435, 1160 cm^{-1}; NMR δ 5.90–5.05 (m, 2 H), 3.66 (s, 3 H), 3.00–0.80 (m, 13 H); exact mass calcd for $C_{11}H_{18}O_2$ m/z 182.1302, found 182.1292.

Methyl 2-acetoxycyclooctylacetate (23): IR 2925, 2860, 1735, 1435, 1365, 1250, 1165, 1020 cm^{-1}; NMR δ 4.90 (m, 1 H), 3.66 (s, 3 H), 2.01 (s, 3 H), 2.50–2.1 (m, 2 H), 2.0–1.0 (m, 13 H).

Mixture of 2- and 3-cyclooctenol acetates (24 and 25):[43,44] IR 3025, 2925, 2855, 1735, 1450, 1370, 1240, 1030 cm^{-1}; NMR δ 4.43 (d, 1 H, J = 5.9 Hz), 3.00–1.90 (m, 5 H), 1.80–0.95 (m, 6 H); exact mass calcd for $C_9H_{12}O_2$ m/z 152.0834, found 152.0838.

(3a*α*,4*β*,7*β*,7a*α*)-Hexahydro-4,7-methanobenzofuran-2(3*H*)-one (26):[45] IR 2960, 2875, 1780, 1460, 1410, 1360, 1170, 1025, 885, 870, 680 cm^{-1}; NMR δ 4.43 (d, 1 H, J = 5.9 Hz), 3.00–1.90 (m, 5 H), 1.80–0.95 (m, 6 H); exact mass calcd for $C_9H_{12}O_2$ m/z 152.0834, found 152.0838.

Methyl 2-*endo*-acetoxy-3-*exo*-bicyclo[2.2.1]heptylacetate (27-Me ester): IR 2950, 2885, 1733, 1435, 1375, 1240, 1145, 1115 cm^{-1}; NMR δ 4.58 (br t, 1 H, J = 5 Hz), 3.67 (s, 3 H), 2.00 (s, 3 H), 2.00 (s, 3 H), 2.60–0.90 (m, 11 H); exact mass calcd for $C_{12}H_{18}O_4$ m/z 226.1200, found 226.1211.

Methyl 2-*exo*-bicyclo[2.2.1]heptylacetate (28-Me ester): IR 2950, 2870, 1737, 1435, 1255, 1195, 1160, 998, 800 cm^{-1}; NMR δ 3.66 (s, 3 H), 2.19 (d, 1 H, J = 2 Hz), 2.10 (s, 1 H), 2.0–1.65 (m, 2 H), 1.55–0.90 (m, 9 H); exact mass calcd for $C_{10}H_{16}O_2$ m/z 168.1146, found 168.1140.

Methyl 2-*exo*-acetoxy-7-*syn*-bicyclo[2.2.1]heptylacetate (29-Me ester): IR 2950, 2875, 1736, 1435, 1375, 1245, 1015 cm^{-1}; NMR δ 4.53 (dd, 1 H, J = 7, 3 Hz), 3.68 (s, 3 H), 2.0 (s, 3 H), 2.35–1.05 (m, 11 H, with major peak at 2.10), exact mass calcd for $C_{12}H_{18}O_4$ m/z 226.1200, found 226.1209.

2-*exo*-Bicyclo[2.2.1]heptanol acetate (30):[46] IR 2960, 2870, 1735, 1375, 1360, 1250, 1240, 1070, 1015 cm^{-1}; NMR δ 4.53 (br d, J = 7 Hz), 2.40–2.1 (br s, 2 H), 2.02 (s, 3 H), 1.90–1.00 (m, 8 H).

Dihydro-5-methyl-5-phenyl-2(3*H*)-furanone (31): IR 3060, 3030, 2980, 1780, 1495, 1445, 1295, 1240, 1210, 1130, 1065, 940, 765, 700 cm^{-1}; NMR δ 7.35 (s, 5 H), 2.85–2.15 (m, 4 H), 1.71 (s, 3 H); exact mass calcd for $C_{11}H_{12}O_2$ $(m + 1)/z$ 177.0912, found 177.0918, calcd m/z 176.0834, found 176.0835.

Methyl 4-phenylbut-4-enoate (32-Me ester): IR 3060, 3020, 2990, 2950, 1735, 1670, 1605, 1495, 1435, 1280, 1200, 1160, 1110, 900, 780, 710 cm^{-1}; NMR δ 7.65–7.15 (m, 5 H), 5.32 (d, 1 H, J = 7 Hz), 5.02 (br d, 1 H, J = 7 Hz), 3.65 (s, 3 H), 3.0–2.6 (m, 2 H), 2.6–2.3 (m, 2 H).

Dihydro-5-phenyl-5-((methoxycarbonyl)ethyl)-2(3*H*)-furanone (33-Me ester): IR 3060, 3030, 2950, 1775, 1735, 1445, 1300, 1260, 1190, 1160, 935, 765, 705 cm^{-1}; NMR δ 7.34 (s, 5 H), 3.59 (s, 3 H), 2.70–2.4 (m, 4 H), 2.4–1.9 (m, 4 H); exact mass calcd for $C_{14}H_{16}O_4$ m/z 248.1044, found 248.1063.

2-Phenyl-2-propenol acetate (34): IR 3080, 3060, 3030, 2975, 1735, 1445, 1380, 1365, 1230, 1025, 760, 700 cm^{-1}; NMR δ 7.60–6.90 (m, 5 H), 5.95–4.30 (m, 4 H), 2.08 (s, 3 H).

Dihydro-5,5-diethyl-4-methyl-2(3*H*)-furanone (35): IR 2980, 2945, 2890, 1770, 1465, 1230, 960 cm^{-1}; NMR (80 MHz) δ 2.85–1.85 (m, 3 H), 1.90–1.40 (m, 4 H), 1.30–0.70 (m, 9 H); (300 MHz) δ 2.68 (dd, 1 H, J = 17.10, 8.35 Hz), 2.56–2.42 (m, 1 H), 2.25 (dd, 1 H, J = 17.10, 9.20 Hz), 1.78–1.48 (m, 4 H), 1.08 (d, 3 H, J = 7.00 Hz), 0.96 (t, 3 H, J = 7.49 Hz), 0.93 (t, 3 H, J = 7.53 Hz); exact mass calcd for $C_8H_{16}O_2$ m/z 156.1146, found 156.1147.

***cis*-3,3a,4,8b-Tetrahydro-2*H*-indeno[1,2-*b*]furan-2-one (36)**:[47] IR 3070, 3020, 2930, 2850, 1772, 1165, 950, 760, 740 cm^{-1}; NMR δ 7.57–7.07 (m, 4 H), 5.38 (d, 1 H, J = 7 Hz), 3.50–2.05 (m, 5 H).

***trans*-Dihydro-1*H*-indene-1,2-diol diacetate (37)**:[48] IR 3080, 3030, 2960, 1740, 1245, 1225, 1035, 750 cm^{-1}; NMR δ 7.45–7.03

(37) Lethbridge, A.; Norman, R. O. C.; Thomas, C. B.; Parr, W. J. E. *J. Chem. Soc., Perkin Trans 1* **1975**, 231–241.
(38) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1980**, *45*, 4111–4117. Herz, W.; Glick, L. A. *Ibid.* **1963**, *28*, 2970–2975.
(39) Jankowski, K.; Daigle, J. Y. *Can. J. Chem.* **1971**, *49*, 2594–2597.
(40) Baeckvall, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 4959–4960.
(41) Bensel, N.; Marschall, H.; Weyerstahl, P. *Chem. Ber.* **1975**, *108*, 2697–2702. Uusvuorio, R.; Hase, T.; Suokas, E. *Acta Chem. Scand., Ser. B.* **1978**, *B32*, 531–535.
(42) Moon, S.; Kolesar, T. F. *J. Org. Chem.* **1974**, *39*, 995–998.
(43) Cope, A. C.; Kinter, M. R.; Keller, R. T. *J. Am. Chem. Soc.* **1954**, *76*, 2757–2760.
(44) Crandall, J. K.; Arrington, J. P.; Mayer, C. F. *J. Org. Chem.* **1971**, *36*, 1428–1433.
(45) Sauers, R. R.; Sonnet, P. E. *Tetrahedron* **1964**, *20*, 1029–1035.
(46) Authentic sample available.
(47) House, H. O.; Babad, H.; Toothill, R. B.; Noltes, A. W. *J. Org. Chem.* **1962**, *27*, 4141–4146. Bergman, E. D.; Hoffman, E. *Ibid.* **1961**, *26*, 3555–3556. Regioisomer: Jeffs, P. W.; Molina, G.; Cass, M. W.; Cortese, N. A. *Ibid.* **1982**, *47*, 3871–3875. Dalton, L. K.; Elmes, B. C. *Aust. J. Chem.* **1975**, *25*, 2261–2262.
(48) Hatsui, T.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2655–2658. Imuta, M.; Ziffer, H. *J. Org. Chem.* **1978**, *43*, 4540–4542. Austin, R. A.; Lillya, C. P. *Ibid.* **1969**, *34*, 1327–1333.

(m, 4 H), 6.18 (d, 1 H, J = 3.6 Hz), 5.38 (ddd, 1 H, J = 7.2, 4.8, 3.6 Hz), 3.47 (dd, 1 H, J = 16.5, 7.2 Hz), 2.82 (dd, 1 H, J = 16.5, 4.8 Hz), 2.09 (s, 3 H), 2.05 (s, 3 H).

***cis*-Dihydro-1*H*-indene-1,2-diol diacetate (38)**:[48] IR 3050, 3030, 2960, 1740, 1370, 1250, 1065, 755, 735 cm^{-1}; NMR δ 7.45–7.10 (m, 4 H) 6.18 (d, 1 H, J = 5.4 Hz), 5.65–5.37 (m, 1 H), 3.14 (dd, 2 H, J = 6.2, 1.8 Hz), 2.08 (s, 3 H), 2.05 (s, 3 H); mp 47.5–48.5 °C (lit. mp 48.0–48.5 °C).

Inden-2-ol acetate (39): IR 3060, 3020, 2930, 1740, 1230, 1025, 750, 715 cm^{-1}; NMR δ 7.60–6.95 (m, 4 H), 6.79 (br s, 1 H), 3.41 (br s, 2 H), 2.10 (s, 3 H).

***trans*-Dihydro-4-methyl-5-phenyl-2(3*H*)-furanone (40)**:[28] IR 3070, 3035, 2965, 2930, 1785, 1495, 1455, 1280, 1215, 1140, 1000, 945, 755, 700 cm^{-1}; NMR δ 7.34 (s, 5 H), 4.91 (d, 1 H, J = 8.0 Hz), 2.90–1.95 (m, 3 H), 1.16 (d, 3 H, J = 6.2 Hz); exact mass calcd for $C_{11}H_{12}O_2$ m/z 176.0834, found 176.0833.

***cis*-Dihydro-4-methyl-5-phenyl-2(3*H*)-furanone (41)**:[28] IR 3060, 3030, 2970, 2930, 1780, 1495, 1455, 1240, 1155, 985, 750, 700 cm^{-1}; NMR δ 7.65–7.05 (m, 5 H), 5.55 (d, 1 H, J = 6 Hz), 3.00–2.05 (m, 3 H), 0.69 (d, 3 H, J = 7.0 Hz).

***trans*-Dihydro-4-phenyl-5-methyl-2(3*H*)-furanone (42)**:[28] IR 3070, 3030, 2980, 2930, 1780, 1495, 1455, 1385, 1200, 1170, 1070, 940, 755, 700 cm^{-1}; NMR δ 7.60–7.05 (m, 5 H), 4.53 (d, 1 H, J = 8.3 Hz), 3.4–3.05 (m, 1 H), 2.9–2.65 (m, 2 H), 1.42 (d, 3 H, J = 6.1 Hz).

Methyl 4-hydroxy-4-phenyl-5-methylbutanoate (threo/erythro mixture, 1.5:1; 43-Me ester):[49] IR 2970, 2930, 2850, 1775, 1435, 1370, 1235, 1020, 760, 700 cm^{-1}; NMR δ 7.30 (br s, 5 H), 5.69 (d, 0.4 H, J = 6 Hz), 5.54 (d, 0.6 H, J = 7.2 Hz), 3.66 (s, 1.8 H), 3.63 (s, 1.2 H), 2.75–1.95 (m, 3 H), 2.08 (s, 1.2 H), 2.04 (s, 1.8 H), 0.96 (d, 1.2 H, J = 6.7 Hz), 0.86 (d, 1.8 H, J = 6.6 Hz); exact mass calcd for $C_{13}H_{18}O_4$ m/z 250.1200, found 250.1195.

***threo*-1-Phenyl-1,2-propanediol diacetate (44)**:[50] IR 3070, 3040, 2990, 2949, 1737, 1455, 1370, 1240, 1040, 1020, 760, 700 cm^{-1}; NMR δ 7.33 (br s, 5 H), 5.75 (d, 1 H, J = 7.2 Hz), 5.22 (dq, 1 H, J = 7.2, 6.4 Hz), 2.07 (s, 3 H), 2.02 (s, 3 H), 1.08 (d, 3 H, J = 6.4 Hz).

***erythro*-1-Phenyl-1,2-propanediol diacetate (44)**: IR 3070, 3040, 2990, 2940, 1735, 1495, 1455, 1370, 1235, 1020, 755, 700 cm^{-1}; NMR δ 7.33 (br s, 5 H), 5.87 (d, 1 H, J = 4.5 Hz), 5.20 (dq, 1 H, J = 4.5, 6.4 Hz), 2.13 (s, 3 H), 1.99 (s, 3 H), 1.16 (d, 3 H, J = 6.4 Hz).

***2-threo*-1-Phenyl-1,2-propanediol acetate (45)**: IR 3450, 3060, 3030, 2980, 2935, 1730, 1455, 1370, 1240, 1040, 760, 700 cm^{-1}; NMR δ 7.33 (br s, 5 H), 5.04 (dq, 1 H, J = 3.5, 7 Hz), 4.60 (d, 1 H, J = 7 Hz), 2.80 (br, 1 H), 2.06 (s, 3 H), 1.10 (d, 3 H, J = 6.4 Hz).

***2-erythro*-1-Phenyl-1,2-propanediol acetate (45)**: IR 3490, 3060, 3030, 2970, 2930, 1730, 1455, 1370, 1240, 750, 700 cm^{-1}; NMR δ 7.65–7.05 (m, 5 H), 5.07 (dq, 1 H, J = 4, 6.5 Hz), 4.82 (d, 1 H, J = 4 Hz), 2.04 (s, 3 H), 1.15 (d, 3 H, J = 6.5 Hz), OH not observed.

***trans*-Dihydro-4-methyl-5-(butoxycarbonyl)-2(3*H*)-furanone (46)**: IR 2960, 2930, 2875, 1790, 1745, 1460, 1270, 1145, 1095, 1050 cm^{-1}; NMR δ 4.49 (d, 1 H, J = 4.7 Hz), 4.21 (t, 2 H, J = 6.4 Hz), 2.90–1.85 (m, 3 H), 1.80–1.05 (m, 7 H), 1.29 (d, 3 H, J = 6.6 Hz), 0.94 (t, 3 H, J = 6.3 Hz); exact mass calcd for $C_{10}H_{16}O_4$ $(m + 1)/z$ 201.1122, found 201.1120, calcd m/z 200.1044, found 200.1041.

***trans*-Dihydro-5-methyl-4-(butoxycarbonyl)-2(3*H*)-furanone (47)**: IR 2960, 2935, 2875, 1785, 1735, 1455, 1420, 1385, 1260, 1195, 1055, 940 cm^{-1}; NMR δ 4.85 (quint, 1 H, J = 6 Hz), 4.16 (t, 2 H, J = 6.4 Hz), 3.20–2.62 (m, 3 H), 1.85–1.10 (m, 7 H), 1.51 (d, 3 H, J = 6.2 Hz), 0.94 (t, 3 H, J = 6.3 Hz); exact mass calcd for $C_{10}H_{16}O_4$ $(m + 1)/z$ 201.1122, found 201.1140.

***trans*-Dihydro-5-phenyl-4-(carbomethoxy)-2(3*H*)-furanone (48)**:[51] IR 3070, 3040, 3010, 2960, 1785, 1735, 1495, 1435, 1360, 1310, 1260, 1195, 1005, 765, 695 cm^{-1}; NMR δ 7.36 (s, 5 H), 5.64 (d, 1 H, J = 6.8 Hz), 3.75 (s, 3 H), 3.33 (dd, 1 H, J = 6.8, 2.9 Hz), 3.02 (d, 1 H, J = 11 Hz), 2.76 (dd, 1 H, J = 11, 2.9 Hz), exact mass calcd for $C_{12}H_{12}O_4$ m/z 220.0732, found 220.0740.

***cis*-Dihydro-5-phenyl-4-(carbomethoxy)-2(3*H*)-furanone (49)**:[51] IR 3060, 3030, 3005, 2950, 1785, 1732, 1495, 1437, 1380, 1210, 1170, 1005, 750, 700 cm^{-1}; NMR δ 7.55–6.93 (m, 5 H), 5.75 (d, 1 H, J = 7.8 Hz), 3.28 (s, 3 H), 3.70 (br dt, 1 H, J = 6, 9 Hz), 5.10 (dd, 1 H, J = 18, 6 Hz), 2.75 (dd, 1 H, J = 18, 9 Hz).

***trans*-Dihydro-4-phenyl-5-(carbomethoxy)-2(3*H*)-furanone (50)**: IR 3060, 3035, 3005, 2960, 1785, 1735, 1495, 1435, 1370, 1005, 765, 695 cm^{-1}; NMR δ 7.65–7.10 (m, 5 H), 4.91 (d, 1 H, J = 4.6 Hz), 3.82 (s, 3 H), 4.2–3.4 (m, 1 H), 3.05 (dd, 1 H, J = 18, 9 Hz), 3.62 (dd, 1 H, J = 18, 6 Hz).

1-Hydroxy-4-methyl-3-penten-2-one acetate (51): IR 2980, 2935, 1750, 1705, 1630, 1445, 1370, 1235, 1030 cm^{-1}; NMR δ 6.05 (septet, 1 H, J = 1.3 Hz), 4.65 (s, 2 H), 2.19 (d, 3 H, J = 1.1 Hz), 2.17 (s, 3 H), 1.91 (d, 3 H, J = 1.2 Hz), exact mass calcd for $C_8H_{12}O_3$ m/z 156.0783, found 156.0795.

Acknowledgment. We are indebted to the National Science Foundation and the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. J.R.P. thanks the 3-M Company and the University of Minnesota Graduate School for fellowships.

(49) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.
(50) Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc. B* **1968**, 994–1005.
(51) Bourelle-Wargnier, F.; Gastambide, B. *Bull. Soc. Chim. Fr.* **1965**, 1405–1411.

6-(Methoxymethylene)penicillanic Acid: A New β-Lactamase Inactivator

Daniel G. Brenner

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Received August 21, 1984

The β-lactamase inactivator 6-(methoxymethylene)penicillanic acid is the first compound in a new class of penams having a heteroatom-substituted methylene group at the 6-position conjugated to the β-lactam carbonyl. Treatment of benzyl 6-oxopenicillanate with the anion of methoxy(trimethylsilyl)methane gives a pair of β-silyl alcohols. Quantitative acetylation of either of the alcohols and subsequent fluoride-promoted elimination of acetate and trimethylsilyl fluoride yields an equilibrium mixture of the *Z* and *E* isomers of the title compound. Close examination of the elimination reaction by ^{1}H NMR permitted the assignment of the chirality in the C-6 side chain of the β-silyl alcohols that was confirmed by X-ray crystallographic analysis. After separation of the enol ether geometrical isomers, it was found that whereas the *E* isomer does not interact perceptibly with the purified RTEM-2 β-lactamase from *E. coli*, the *Z* isomer irreversibly inactivates the enzyme.

The enzyme β-lactamase catalyzes the hydrolysis of β-lactam antibiotics to the therapeutically impotent penicillanic acids, and bacterial strains that possess this enzyme are generally resistant to the killing effects of hydrolytically labile but otherwise potent β-lactam antibiotics. β-Lactamase is therefore regarded as an important target, in the effort to retain the clinical utility of susceptible but powerfully therapeutic β-lactams. The past

0022-3263/85/1950-0018$01.50/0