The interpretation is consistent with hydrogen-bonding effects observed in an ^{17}O NMR and kinetic study[9] on α-azo hydroperoxides. The ^{17}O NMR data (solvent dependence) seemed to correlate with the kinetics data[9] for ionic oxidation in the varying solvents. Of particular interest were the results for methanol. In this protic medium, the ionic oxidations showed small increases in k_2 values. The ^{17}O NMR data on the ^{17}O-enriched α-azo hydroperoxides showed intermolecular hydrogen-bonding between the solvent and the peroxy oxygen. This suggested that hydrogen bonding with methanol was responsible for the small intermolecular catalytic effects noted on the oxidations.

Cyclic α-azo hydroperoxides were shown[3c] to be of similar reactivities and selectivities to those of flavin 4a-hydroperoxide model compounds[10] in N- and S-oxidations. The present results show that the reactivity of a hydroperoxide in oxygen atom transfer reactions can be greatly increased in intramolecular acid catalysis. Stable flavin 4a-hydroperoxides[10] and peracids are often taken[11] as chemical models for flavin monooxygenase activity. It is tempting to speculate that catalysis due to an acidic group in the active site of a flavin monooxygenase might also increase the reactivity of flavin 4a-hydroperoxides.

Acknowledgment is made to the Dreyfus Foundation and to the GSU Research Fund for support of this research.

Registry No. 1, 97783-03-4; 2, 97783-04-5; 3, 97783-05-6; 4, 2829-34-7; o-HOC_6H_4CH=NNHPh, 614-65-3; o-$MeOC_6H_4CH$=NNHPh, 21968-29-6; 2-HO-5-ClC_6H_3CH=NNHPh, 97783-06-7; 2,3-dimethyl-2-butene, 563-79-1; p-methoxythioanisole, 1879-16-9.

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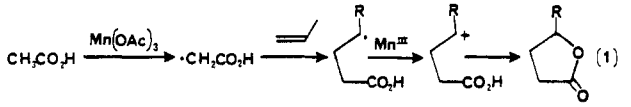
Manganese(III)-Based Oxidative Free-Radical Cyclization. Synthesis of (±)-Podocarpic Acid

Summary: The oxidative cyclization of unsaturated β-keto esters with $Mn(OAc)_3$ is described.

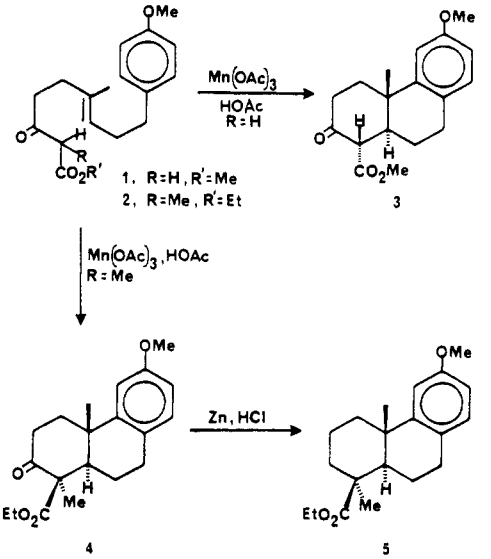
Sir: The use of free-radical carbon-carbon bond-forming reactions is undergoing a renaissance.[2] These reactions are being developed into powerful tools for the synthesis of complex targets. In particular, free-radical cyclizations of alkenes have become a valuable method for the synthesis of polycyclic compounds.[3] Unfortunately, these cyclizations are typically terminated by hydrogen atom transfer, which reduces the functionality in the product, usually rendering the initially unsaturated carbons inaccessible to further manipulation. Oxidative free-radical cyclization, in which the reaction is terminated by oxidation of the radical center to a carbocation that reacts with a nucleophile or loses a proton to give a new alkene, would therefore be a powerful addition to free-radical-based synthetic methods.[4]

The well-known, but underutilized, oxidative addition of acetic acid to alkenes with 2 equiv of manganese(III) acetate to give a γ-lactone (eq 1) provides the basis for a



solution to this problem.[5] Oxidative cyclization of unsaturated acids is not possible, since the solvent, acetic acid, is oxidized preferentially. Fortunately, unsaturated β-keto esters are suitable substrates, since they are oxidized much more rapidly than acetic acid.[5,6,7] While this work was in progress, Corey and Kang reported that unsaturated β-keto acids undergo oxidative free-radical cyclization on treatment with manganese(III) acetate to form both a cyclopentane ring and a γ-lactone.[8]

Treatment of β-keto ester 1[9] (0.1 M) in acetic acid with 2 equiv of $Mn(OAc)_3$ (15 min at 15-20 °C, 45 min at 20 °C) gives a 70% yield of the tricyclic adduct 3, mp 145-146



°C (lit.[11] mp 146-147 °C), which is a late intermediate in Welch's podocarpic acid synthesis.[11] $Mn(OAc)_3$ presum-

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(6) For a detailed study of this reaction, see: Fristad, W. E.; Peterson, J. R. *J. Org. Chem.* **1985**, *50*, 10.

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(8) Corey, E. J.; Kang, M.-C. *J. Am. Chem. Soc.* **1984**, *106*, 5384.

(9) All starting materials were prepared by alkylation of the dianion of the corresponding acetoacetate ester in 60-90% yield.[10] The allylic bromide used for the preparation of 1 and 2 was prepared from 3-(4-methoxyphenyl)-1-propanol in four steps in 51% overall yield.

(10) Weiler, L.; Huckin, S. N. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

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0022-3263/85/1950-3659$01.50/0

ably oxidizes the manganese enolate of the β-keto ester to the enol radical which adds to the double bond to give a tertiary radical which adds to the aromatic ring.[5d] The resulting cyclohexadienyl radical is then oxidized by a second equivalent of $Mn(OAc)_3$ to the cation which loses a proton to regenerate the aromatic ring. It is also possible that the radical is oxidized to a cation earlier in the cyclization sequence. The stereospecific synthesis of **3** establishes that addition to the double bond is stereospecifically trans in accord with other radical polycyclizations.[3c,4,12] The stereochemistry at C-4 is not established in the cyclization but by equilibration of the product.

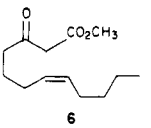
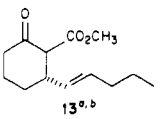
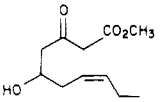
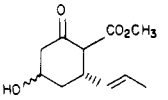
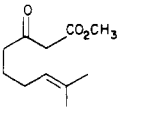
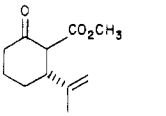
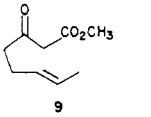
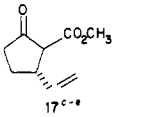
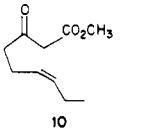
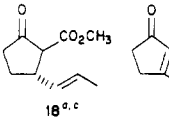
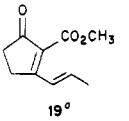
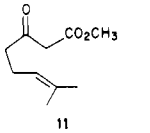
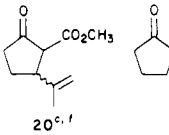
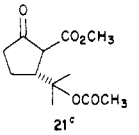
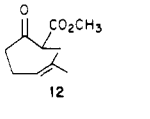
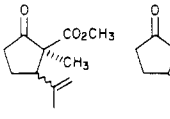
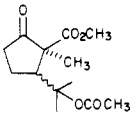
We therefore turned our attention to the β-keto ester **2**, in which the kinetic product cannot isomerize. Determination of the structure of the cyclized products by chemical means was expected to be straightforward regardless of the stereochemical outcome since the product **4** with a 4β-carbethoxy group can be converted to a known podocarpic acid derivative[13] by reductive removal of the 3-keto group, and the product with a 4α-carbethoxy group can be converted to an intermediate in van Tamelen's aphidicolin synthesis by reduction of both the ketone and ester groups to give the corresponding diol.[14] Oxidative cyclization of **2** (0.2 M) in acetic acid with 2 equiv of $Mn(OAc)_3$ (15–20 °C, 1 h) gives a 50% yield of **4**, mp 88–89 °C, uncontaminated with other tricyclic products. Analysis of the ^1H and ^{13}C NMR spectra[15] suggested that the product had a 4β-carbethoxy group. The structure was confirmed by Clemmensen reduction,[16] which gives a 60% yield of **5**, mp 56–58 °C (lit.[13] mp 58–59 °C), which was spectroscopically identical with an authentic sample.[17] This constitutes a formal total synthesis of (±)-podocarpic acid since (±)-**5** has been converted to (±)-podocarpic acid.[13]

The stereochemistry of **4** indicates that the cyclization proceeds via an extended enol radical to form ring A in the chair form or via an enol radical in the U form to form ring A as a boat. Further studies are needed to delineate the origin of this selectivity. Attempted oxidative cyclization of **2** with benzoyl peroxide at 80–100 °C gives only trace amounts of **4**.[3c]

The oxidative cyclizations of several simple unsaturated β-keto esters shown in Table I establish that this reaction is useful for the formation of cyclohexanones and cyclopentanones containing unsaturated substituents in the 3-position. The radical formed in the cyclization is oxidized to a carbocation which, in the absence of a free carboxylic acid, loses a proton to form an alkene or reacts with solvent to give an acetate. These results differ markedly from those of Corey and Kang who found that the cyclizations of related β-keto acids are terminated by the formation of a γ-lactone[8] and from those of Heiba and Dessau who found that the intermolecular oxidative addition of β-keto esters with alkenes leads to dihydrofurans.[5e] The oxidative cyclizations of **6–10** (0.1 M) are best accomplished in acetic acid with 2 equiv of $Mn(OAc)_3$ and 1 equiv of $Cu(OAc)_2$[5d,18] for 1 h at 60 °C. In the absence of Cu(II) the radical formed on cyclization abstracts a hydrogen atom faster than it is oxidized.[5d,18] Optimal yields in the cyclizations of **11** and **12** (0.1 M) are obtained with $Mn(OAc)_3$ formed in situ from $KMnO_4$ and $Mn(OAc)_2$[19] in a 75:13:19 w/w/w mixture of acetic acid, potassium acetate, and acetic anhydride as solvent for 1 h at 60 °C.

The results shown in Table I indicate that the reaction is more useful for the preparation of cyclohexanones than cyclopentanones. Keto ester **13** is produced in very good

Table I. Oxidative Free-Radical Cyclization of Unsaturated β-Keto Esters

unsaturated β-keto ester	products	% yield[h]
 **6**	 **13**[a,b]	75
 **7**	 **14**, α-OH[a,b] **15**, β-OH[a,b]	**14**, 41 (45) **15**, 8 (9)
 **8**	 **16**[b]	41
 **9**	 **17**[c-e]	21 (25)
 **10**	 **18**[a,c]  **19**[a]	**18**, 36 (45) **19**, 10 (12.5)
 **11**	 **20**[c,f]  **21**[c]	**20**, 8 **21**, 10
 **12**	 **22**[g]  **23**[g]	**22**, 27 **23**, 20

[a] This (*Z*)-alkene gives a product in which an (*E*)-alkene has been formed stereospecifically. [b] Exists as a mixture of keto and enol tautomers. [c] Exists as a mixture of trans and cis isomers. [d] Taber, D.; Petty, E. *J. Org. Chem.* **1982**, *47*, 4808. [e] 5% of a mixture of methyl 2-hydroxy-6-methylbenzoate, and the corresponding dihydro compounds formed by initial attack of the enol radical on the other end of the double bond were also isolated. [f] Trost, B. M.; Vloduchick, W. C. *J. Org. Chem.* **1979**, *44*, 148. [g] Formed as a 3:2 mixture of β:α isopropenyl isomers. [h] % Yield based on recovered starting material in parentheses.

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(15) Wenkert, E.; Afonso, A.; Beak, P.; Carney, R. W. J.; Jeffs, P. W.; McChesney, J. D. *J. Org. Chem.* **1965**, *30*, 713. Nishida, T.; Wahlberg, I.; Enzell, C. R. *Org. Magn. Reson.* **1977**, *9*, 203. Wehrli, F. W.; Nishida, T. *Prog. Chem. Org. Nat. Prod.* **1979**, *36*, 1–228.
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(17) Prepared from the commercially available methyl ester by saponification and treatment with diazoethane.
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(19) Lux, H. In "Handbook of Preparative Inorganic Chemistry"; Brauer, G., Ed.; Academic Press: New York, 1965; p 1470. Heiba, E. I.; Dessau, R. M.; Williams, A. L.; Rodewald, P. G. *Org. Synth.* **1983**, *61*, 22.

yield, and the sensitive β-hydroxy ketones **14** and **15** are produced in 49% yield with 5:1 selectivity for the equatorial alcohol.

Yields are lower when either the alkene or β-keto ester of the adduct reacts further. The terminal double bonds of **16**, **17**, **20**, and **22** are more susceptible to further attack by electrophiles or electrophilic radicals, which reduces the yield. The β-keto ester moiety of cyclopentanones **17–21** oxidizes more readily than that of cyclohexanones **13–16** at a rate competitive to that of the starting acyclic β-keto ester.[20] The dienone **19** is a product of this overoxidation. Similar products are probably formed from **17** and **20** but undergo polymerization. Oxidative free-radical cyclization of **12** (47%) proceeds in much higher yield than that of **11** (18%), since overoxidation of the β-keto ester is blocked by the methyl group.

These results establish that oxidative free-radical cyclization using $Mn(OAc)_3$ is a valuable method for initiating polyolefin cyclization and is a useful approach for the formation of six- and five-membered carbocycles. Further studies of these reactions are in progress.

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Registry No. **1**, 97690-35-2; **2**, 97690-36-3; **3**, 41437-69-8; **4**, 97690-37-4; **5**, 97690-38-5; **6**, 97690-39-6; **7**, 97690-40-9; **8**, 78249-27-1; **9**, 62344-14-3; **10**, 22617-64-7; **11**, 53067-23-5; **12**, 97690-41-0; **13**, 97690-42-1; **14**, 97690-43-2; **15**, 97690-44-3; **16**, 97690-45-4; **17** (isomer 1), 83221-16-3; **17** (isomer 2), 97690-46-5; **18** (isomer 1), 97690-47-6; **18** (isomer 2), 97747-18-7; **19**, 97690-48-7; **20** (isomer 1), 97690-49-8; **20** (isomer 2), 85642-71-3; **21** (isomer 1), 97690-50-1; **21** (isomer 2), 97690-51-2; **22** (isomer 1), 97690-52-3; **22** (isomer 2), 97690-53-4; **23** (isomer 1), 97690-54-5; **23** (isomer 2), 97690-55-6; $Mn(OAc)_3$, 993-02-2; (±)-podocaspic acid, 15292-90-7.

(20) The relative reactivity of the β-keto esters may correspond to the percent of the keto form present a equilibrium. Acetoacetate and 2-cyclopentanone carboxylate esters are largely ketonic. 2-Oxocyclohexanecarboxylate esters are largely enolic. See: Rhoads, S. J. *J. Org. Chem.* **1966**, *31*, 171. Kol'tsov, A. I.; Kheifets, G. M. *Russ. Chem. Rev. (Engl. Transl.)* **1971**, *40*, 773.

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Relationship of Aromatic Nitro Group Torsion Angles with ^{17}O Chemical Shift Data

Summary: The ^{17}O chemical shifts of seven aromatic nitro groups have been shown, for the first time, to vary with the torsion angle that describes the orientation of the nitro group with respect to the atoms of the aromatic ring. A quantitative relationship between ^{17}O chemical shift data and the torsion angle is reported.

Sir: ^{17}O nuclear magnetic resonance spectroscopy is becoming an increasingly important method in organic chemistry.[1] Despite poor receptivity, the large chemical shift range for this nucleus makes it particularly attractive for examining the influences of subtle changes in molecular structure. We report a relationship between the ^{17}O chemical shift data and the average torsional angle that describes the orientation of the nitro group and the aromatic ring as approximated by X-ray diffraction data.

The influence of electronic effects on ^{17}O chemical shifts of meta- and para-substituted nitrobenzenes has recently been well documented.[2] However, despite the fundamental interest in the molecular structure of complex aromatic nitro compounds[3] and the limited understanding of the role played by sterically crowded aromatic nitro groups in compounds that display important biological activity,[4] no systematic effort to correlate molecular structure for these types of compounds with ^{17}O chemical shifts has appeared. In pioneering work with ^{17}O NMR spectroscopy, Christ and Diehl noted that the chemical shift of *o*-nitrotoluene was downfield from *p*-nitrotoluene by approximately 30 ppm.[5] This shift is presumably, in large part, a result of steric inhibition of conjugation of the nitro group with the aromatic ring.

The ^{17}O chemical shifts of a series of sterically crowded aromatic nitro compounds have been determined[6] as 0.5 M solutions in dried acetonitrile at 75 °C (Table I). Included in the table are chemical shift values determined under these conditions for appropriate unhindered nitro

Table I. ^{17}O Chemical Shifts for Aromatic Nitro Compounds

compd	name	chemical shift,[a]
1	nitrobenzene	575
2	1-nitronaphthalene	605
3	9-nitroanthracene	637
4	2-nitronaphthalene	575
5	1,5-dinitronaphthalene	612
6	1,3-dinitronaphthalene	609, 578
7	1,8-dinitronaphthalene	599
8	*o*-nitrotoluene	602
9	*p*-nitrotoluene	572
10	2,4-dimethylnitrobenzene	597
11	2,3-dimethylnitrobenzene	612
12	2,6-dimethylnitrobenzene	629
13	2,4,6-trimethylnitrobenzene	628
14	2,4,6-tri-*tert*-butylnitrobenzene[b]	657
15	*p*-dinitrobenzene	584
16	*m*-dinitrobenzene	579
17	*o*-dinitrobenzene	609

[a] Taken at 75 °C as 0.5 M solution in dried acetonitrile [2-butanone (0.5%), 558 ± 1 ppm, as an internal check]. [b] Measured at 0.3 M solution because of solubility limitations.

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(6) The ^{17}O spectra, natural abundance, on a JEOL GX-270 spectrometer equipped with a 10-mm broad-band probe operated at 36.5 MHz. The NMR spectra were acquired at natural abundance on 0.5 M solutions in dried acetonitrile (distilled over CaH_2 and stored over molecular sieves) at 75 °C. The chemical shift data were referenced to external water (0.5% 2-butanone was added as an internal check, 558 ± 1 ppm). The instrument settings were either 25-kHz spectral width, 2K data points, 90° pulse angle (28 μs pulse width), 0.3 ms acquisition delay, and 41 ms acquisition time or 30.12-kHz spectral width, 0.25 ms acquisition delay, and 34 ms acquisition time. The spectra were recorded with sample spinning and without lock. The signal-to-noise ratio was improved by applying a 50-Hz exponential broadening factor to the FID prior to Fourier transformation. The data point resolution was improved to ±0.2 ppm by zero filling to 8K data points. Generally, spectra with S/N of about 10/1 were obtained after $\sim 10^5$ scans. Under these conditions, the half-height band widths were 230 ± 30 Hz, except for **3**, 330 Hz, and **14**, 380 Hz. The reproducibility of the chemical shifts is estimated to be ±2 ppm. The nitro compounds studied were commercially available.

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