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Allene epoxidation: synthesis of functionalized lactones by the DMDO oxidation of allenic acids

Jack K. Crandall* and Elisa Rambo

Department of Chemistry, Indiana University, Bloomington, IN 47405-7102, USA

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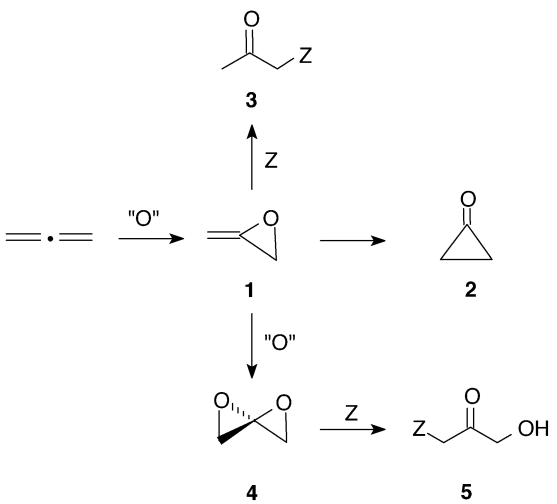
Abstract—A series of allenic carboxylic acids has been converted to functionalized lactones by oxidation–cyclization promoted by dimethyldioxirane. These transformations are rationalized by the involvement of unisolated allene oxide and spirodioxide intermediates. The structures of the starting allenic acids and the reaction conditions determine which of these two intermediate species serves as the source of the isolated products. The use of prepared solutions of the oxidant generally proceed via spirodioxides; whereas in situ reactions normally give products derived from the allene oxides. When products are formed directly from allene oxides, keto lactones are formed. The corresponding spirodioxide intermediates give lactones with appropriately situated α-hydroxyketone moieties. An understanding of the regiochemistry of the epoxidations and the subsequent cyclizations of the reactive intermediates is developed, as are methods for the manipulation of the experimental conditions to favor the desired products.

1. Introduction

The details of the epoxidation chemistry of allenes that are summarized in Scheme 1 have been elaborated in studies dating back to the late 1960s.[1,2] The reaction of allenes with peracids and other oxygen-transfer reagents has been demonstrated to proceed by way of allene oxide (methyleneoxirane) intermediates of type **1**.[3–5] While these reactive species have been shown to isomerize to the more stable, but reactive cyclopropanones of general formulation **2** in certain instances,[5,6] they generally react with nucleophiles present in the reaction mixture to give functionalized ketones of structure **3** as isolated products. Under some oxidation conditions, a second epoxidation reaction can become competitive with other transformations of **1**. This sequential oxidation leads to the formation of spirodioxides (1,4-dioxaspiropentanes) of parent structure **4** as a further reactive intermediate.[7] The intermediate moiety **4** also interacts readily with nucleophiles to give stable acyclic hydroxy ketones of type **5**, in addition to other reaction processes. The overall conversion of allenes to the highly substituted ketones **5** results in an interesting differential functionalization of the three carbons of the original allene carbon triad, a process of some synthetic interest for the rapid incorporation of multiple functionality into a molecule. While examples of compounds of types **1**, **2**, and **4** have been isolated and characterized in special cases, these highly reactive species are ordinarily converted to stable products such as **3** and **5** under the reaction conditions,[3,5] which typically expose them to the carboxylic acids derived from the peracid oxidizing agent. As a result, it has been difficult to control the various competitive and consecutive pathways that occur during the epoxidation of allenes to give a desired product in an efficient manner.

The discovery of a method for the preparation of dilute solutions of the highly reactive and selective oxidizing agent dimethydioxirane[8] (DMDO) has provided a whole new dimension to the epoxidation chemistry of allenes. This remarkable reagent generally permits clean, sequential epoxidation of allenes to isolable spirodioxides,[9] since it is typically used under neutral, non-nucleophilic conditions. These intermediates can then be treated with a range of



Scheme 1.

Keywords: epoxidation of allenes; lactone synthesis; allenic acids; dimethyldioxirane.

* Corresponding author. Fax: +1-812-855-8300; e-mail: jkcran@indiana.edu

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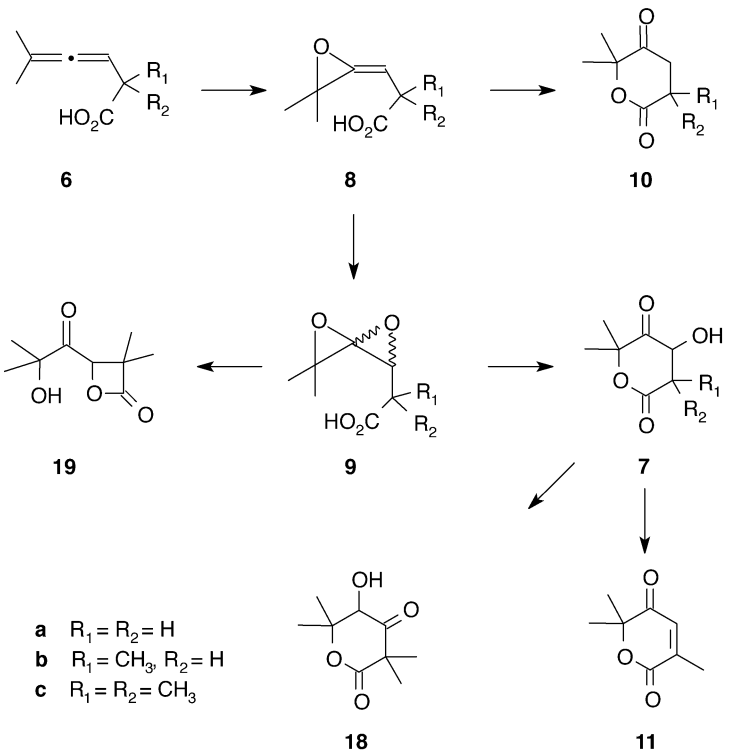
external nucleophiles under non-acidic conditions to produce hydroxy ketones of type **5** possessing a variety of *Z* substituents. The stereochemistry of the spirodioxides derived from substituted allenes can be understood in terms of the normal propensity for the initial epoxidation of DMDO to occur at the more substituted double bond,[10] with stereochemistry being controlled by attack of the epoxidizing agent from the π-face of the double bond situated away from a substituent attached to the non-reacting double bond.[9] The substituted allene oxide intermediate thus generated undergoes a rapid, but frequently stereochemically less discriminating, second epoxidation leading to a substituted spirodioxide. Ring-opening of substituted spirodioxides in the absence of acid appears to take place by nucleophilic attack at the less substituted spirodioxide terminus with inversion of configuration at this carbon site.[9] This is, of course, the normal reactivity pattern for nucleophilic additions to epoxides.

The oxidation of a series of allenic alcohols with DMDO has provided information concerning the behavior of substrates with appended nucleophilic groups.[11] With few exceptions, these reactions proceed by way of spirodioxide intermediates of type **4**, which are not stable under the reaction conditions, but which undergo rapid nucleophilic cyclization. This is not the case for allenic alcohols with other types of oxidizing reagents, which tend to favor reactions of the allene oxide intermediate.[12] Furthermore, the regiochemistry of this intramolecular nucleophilic process is largely controlled by the relative position of the hydroxy group, so as to selectively generate more stable five and six-membered heterocyclic rings. In the present work, we compare the behavior of the analogous carboxylic acids, which can be oxidized either as the free carboxylic acid or in the form of the corresponding carboxylate anion.[13] The presence of a weak acid or a more aggressive nucleophile, respectively, in these two situations might well be expected to influence the oxidation chemistry of these allenic compounds in a significant manner.

2. Results and discussion

The DMDO oxidations of a number of 3,4-dienoic acids were studied in detail. Thus, acid **6a** with *gem*-dimethyl substitution at the remote allenic carbon gave hydroxy lactone **7a** (Scheme 2) in 87% yield. The pathway to **7a** undoubtedly involves sequential formation of allene oxide **8a** and spirodioxide **9a**, prior to intramolecular nucleophilic attack by the pendant carboxylic acid moiety to furnish lactone **7a**. With the specific substitution pattern of allene **6a**, the initial epoxidation is expected to occur preferentially at the more substituted double bond from the π-face opposite to the acid side-chain to give largely the stereoisomer of **8a** shown.[9] The spirodioxide **9a** formed by further epoxidation of **8a** would then have a geometry appropriate for ring-opening with backside participation of the acid function. This is the suggested mechanistic mode of cyclization. However, given the weakly acidic conditions of this reaction, acid-catalyzed ring-opening of **9a** to a carbocation that is subsequently captured by the acid group is an alternative mechanism that cannot be rigorously excluded, although there is no firm evidence for such a pathway.

When acid **6a** was oxidized in situ by incorporating it into a mixture of Oxone,® acetone, aqueous sodium bicarbonate and methylene chloride[11] (conditions for the preparation of DMDO), a new lactone **10a** was formed in 67% yield with little, if any, of its hydroxy analog **7a** being observed. In this



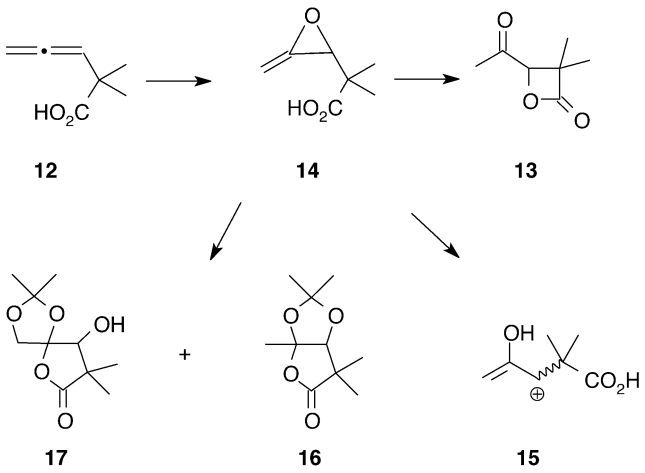
Scheme 2.

instance, cyclization is clearly occurring at the initial allene oxide stage prior to a second epoxidation. Two features of the in situ reaction probably account for this distinct change in the product-forming intermediate from allene oxide **8a** to spirodioxide **9a**. First, **8a** is present as its sodium salt under the in situ reaction conditions, providing for more efficient cyclization onto the epoxide moiety of **8a** by classical displacement at the remote epoxide center by the more nucleophilic carboxylate anion. Secondly, the concentration of DMDO, the presumed oxidant, is undoubtedly much lower under the in situ circumstances, thereby retarding the overall rate of the second epoxidation, once again providing a better opportunity for competing cyclization of allene oxide **8a**. Consistent with this explanation, the oxidation of an acetone solution of acid **6a** that had been previously treated with sodium bicarbonate to generate the corresponding carboxylate anion with a solution of DMDO gave a mixture of the two types of lactones **7a** (52% yield) and **10a** (10% yield). Thus, products derived from cyclization of either the mono or the di-epoxidized intermediates from **6a** can be achieved simply by modifying the oxidation conditions. In situ reactions give the simple lactone **10a**, whereas the use of DMDO solutions leads to the hydroxy lactone **7a**.

The closely related allenic acid **6b**, which possesses an additional methyl group at the 2-position, behaved quite analogously to **6a**. DMDO oxidation of the free acid gave lactone **7b** in 92% yield as a 3:2 mixture of *cis* and *trans* isomers. The assignment of stereochemistry to the minor isomer is based on a 13 Hz coupling constant between the two vicinal protons on the ring in the NMR spectrum of the *trans* compound. (The *cis* isomer has a measured coupling constant of 6 Hz.) Molecular mechanics calculations[14] were used to predict the stable conformations and coupling constants of the two isomers. This verifies that only the *trans* compound is consistent with the large observed coupling constant. Thus, the methyl group at the 2-position has little controlling influence on the stereochemistry of the product as might have been expected. Interestingly, an attempt at silylation of this isomeric mixture with TBDMS triflate and 2,6-lutidine, in order to facilitate separation, resulted in conversion to a mixture of the silylated *trans* alcohol **7b** (50% yield) and the dehydrated lactone **11** (34% yield). Elimination and epimerization accompany the silylation of **7b** under these conditions.

Once again, in situ oxidation gave the less highly functionalized δ-lactone **10b** efficiently (76% yield). Oxidation of the carboxylate anion of **6b** with a solution of DMDO in the presence of $NaHCO_3$ resulted in the formation of a mixture of lactone **10b** with the *cis* and *trans* hydroxy lactones **7b** as found in the previous experiment.

The oxidation chemistry of the terminal allenic acid **12** showed a significantly different pattern (Scheme 3). In this case, product formation from the allene oxide intermediate was dominant, since **12** gave the β-lactone **13** as the major product, regardless of the oxidation conditions: DMDO (52% yield), DMDO plus $NaHCO_3$ (84% yield) and in situ reaction (72% yield). The formation of a strained four-membered ring lactone in this instance is striking, but this selectivity is surely governed by the regiochemistry of the



Scheme 3.

initial epoxidation, which now occurs preferentially at the more substituted, internal double bond of allene **12** to generate allene oxide **14**. While the unsubstituted double bond of allene oxide **14** is expected to undergo epoxidation less readily than that of the more highly substituted analogs discussed above, it is nonetheless surprising that ring-closure of **14** to the strained β-lactone **13** is able to compete so favorably with further epoxidation. The exclusive nucleophilic attack of the both the free acid and the corresponding carboxylate anion at the proximate epoxide site of **14** suggests that lactone formation occurs directly from the intact allene oxide even in the case of the free acid. An alternate route involving prior conversion to hydroxy allyl cation **15** by protonation and ring-opening of **14** would be expected to give at least some of the more stable isomeric δ-lactone, unless the requisite *syn* isomer of **15** is totally inaccessible for some reason. The steric bulk of the acid-bearing side-chain of **15** in this specific case makes it difficult to rule out exclusive reaction through the more stable *anti* isomer of **15**, which can only cyclize to β-lactone **13**. Nonetheless, the simplest explanation consistent with the facts is a single-step nucleophilic displacement for the free acid, as well as the corresponding carboxylate anion.

The addition of *p*-toluenesulfonic acid to a DMDO oxidation of **12** was also examined, in view of the observation that strong acid has been found to encourage the cyclization of the analogous alcohols at the allene oxide stage.[11] In this case, a similar process would involve diverting **14** to the corresponding hydroxy allyl cation **15**. In fact, this reaction gave two unexpected products that had incorporated acetone, as well as a 15% yield of β-lactone **13**. The new solids were assigned as the cyclic ketals **16** (43% yield) and **17** (32% yield) on the basis of their unique spectroscopic properties. While the pathway to these products is not entirely clear, there are a number of logical routes that ketal formation and migration could follow. The more highly oxidized ketal **17** appears to be derived from the further oxidation of **16**, since higher oxidation products of **12** that might lead directly to **17** are not observed in any of the other reactions of **12**.

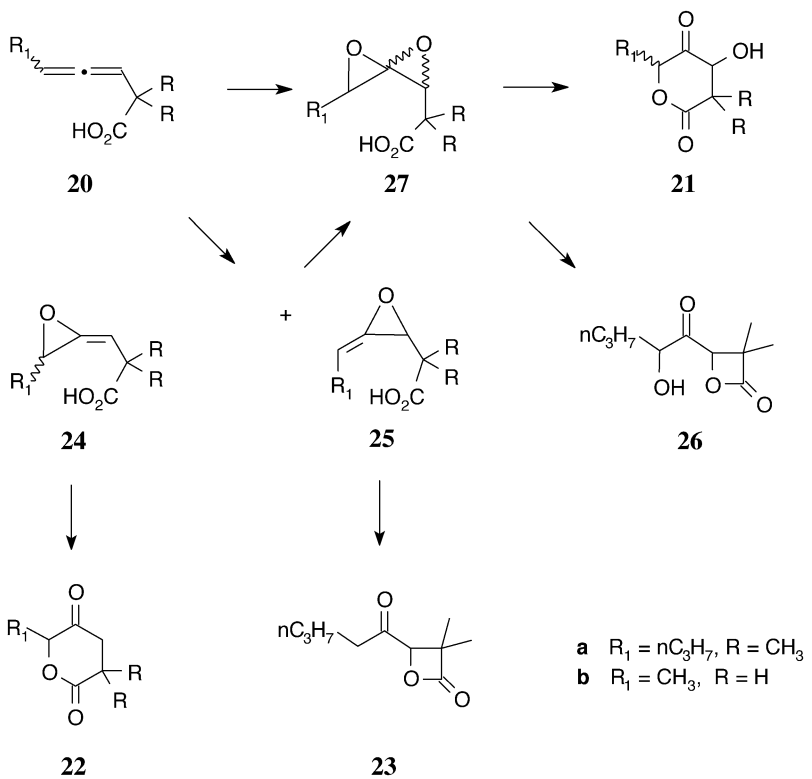
The 3,4-dienoic acid **6c**, with *gem*-dimethyl substitution at both the allene terminus and the 2-position, was found to give crystalline hydroxy lactone **7c** in 96% yield under the

usual DMDO oxidation conditions (Scheme 2). Unexpectedly, flash chromatography on silica gel isomerized **7c** to a secondary product assigned structure **18**. This new lactone **18** could also be prepared in 80% yield simply by stirring **7c** with a slurry of silica gel in THF. Similar isomerizations were noted in our work on the oxidative cyclization of alcohols.[11] This ketol rearrangement undoubtedly involves tautomerization to an enediol intermediate that provides for equilibration of **7c** with isomeric keto alcohol **18**. The displacement of this equilibrium strongly in favor of the 3-keto isomer **18** is remarkable, but finds precedence in related situations.[11,15]

Once again in situ oxidation of **6c** cleanly produced the less highly oxidized lactone **10c** (76% yield). The addition of *p*-toluenesulfonic acid to a DMDO oxidation modified the oxidation to give a mixture of the two types of δ-lactones **7c** and **10c** in a ratio of 1:4. In this case, the presence of a strong acid has diverted some of the allene oxide **8c** to lactone **10c** as anticipated, although the strong acid did not prevent substantial competing epoxidation of **8c** to spirodioxide **9c**, the precursor of lactone **7c**. Unlike the related reaction of **12**, only δ-lactones were formed; the corresponding β-lactones were not observed as significant products.

Interestingly, DMDO oxidation of **6c** in the presence of $NaHCO_3$ resulted in a mixture of δ-lactones **7c** (44% yield) and **10c** (11% yield), along with an 11% yield of a crystalline hydroxy β-lactone **19**. Thus, oxidation of **6c** in the form of its carboxylate anion once again results in some attack at the proximal carbon of the original allene to give the strained lactone **19**. However, this time cyclization to a β-lactone takes place at the stage of spirodioxide intermediate **9c**, where the carboxylate anion has a choice of sites for intramolecular nucleophilic attack. In this instance, the more aggressive carboxylate anion appears to favor β-lactone formation relative to the cyclization of the free acid, which gives only δ-lactone. Geminal dimethylation at the 2-position is probably an important factor in promoting this regiochemistry by the well-known Thorpe–Ingold effect,[16] which may be more effective in orienting the molecule for the more constrained cyclization to the β-lactone relative to that for the δ-lactone. It was also considered that β-lactone **19** might have been derived from a minor stereoisomer of spirodioxide with an inappropriate geometry for intramolecular carboxylate displacement with inversion at the remote site to give hydroxy lactone **7c**. However, little, if any, of the wrong spirodioxide diastereomer is expected from **6c** because of the influence of the sterically large acid-bearing side-chain on epoxidation. The β-lactone **19** was shown to be converted to δ-lactone **7c** upon stirring with K_2CO_3 in acetone. On the other hand, weak acid did not promote this conversion, since exposure to acetic acid in acetone did not result in an observable change in the **7c/19** ratio of a mixture of the two lactones. It is quite conceivable that some of the δ-lactone **7c** that is observed in the oxidation of **6c** with DMDO in the presence of $NaHCO_3$ is derived from base-promoted equilibration of β-lactone **19** and δ-lactone **7c** under the reaction conditions.

Two examples of 3,4-dienoic acids bearing a single substituent at the remote allenic center were also examined (Scheme 4). As expected, DMDO oxidation of acid **20a** with *gem*-dimethyl substitution at the 2-position gave hydroxy δ-lactone **21a** as a mixture of *cis* (36% yield) and *trans* (53% yield) isomers. The lack of stereocontrol, while disappointing, is consistent with previous results that



Scheme 4.

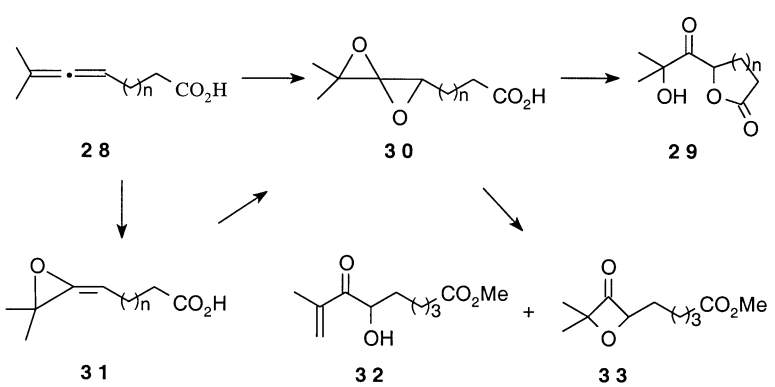
showed poor stereoselection[9] in the formation of spirodioxides from 1,3-disubstituted allenes. Although post-cyclization epimerization at either side of the ketone function would also explain the randomization of stereochemistry here, enolization at the alcohol center would probably be expected to promote transposition of the keto alcohol unit in a manner similar to the **7c** to **18** rearrangement. There is no evidence for significant involvement of such an isomerization during this oxidation reaction, so it is likely that the initial product is a similar mixture.

In situ oxidation of **20a** gave a mixture of the simple δ-lactone **22a** (53% yield) and isomeric β-lactone **23** (53% yield). If it is assumed that ring-closure under the conditions of this reaction occurs by a single-step nucleophilic attack of carboxylate anion on an allene oxide, then the two allene oxide regioisomers **24a** and **25a** that are precursors for **22a** and **23**, respectively, must have been generated in roughly a 2:1 ratio. The dominant stereochemistry of the reactive allene oxides is expected to be that shown in structures **24a** and **25a**, owing to the controlling steric influence of the substitutent on the non-reacting double bond. In both cases backside nucleophilic cyclization is possible. The same degree of substitution at the two double bonds of the allene unit accounts for the relatively low level of regioselectivity in allene oxide formation, although there appears to be a slight discrimination in favor of epoxidation at the double bond with the sterically smaller substituent.

DMDO oxidation of the pre-formed carboxylate salt ($NaHCO_3$) of **20a** generated a mixture of four lactones: **22a** (9% yield), **23** (7% yield), **21a** (37% yield), and a new β-lactone **26** (10% yield). This result again indicates competitive intramolecular carboxylate trapping of the isomeric allene oxides with further oxidation to the diastereomeric spirodioxides **27a** under these conditions. In addition to the *cis* and *trans* hydroxy δ-lactones **21a** that were generated in the simple DMDO oxidation, the hydroxy β-lactone **26** was also obtained from allenic acid **20a** as a 2:1 mixture of diasteromers. This parallels the results with **7c**. Thus, β-lactone formation occurs from both allene oxide and spirodioxide intermediates in the oxidation of **20a** with DMDO and $NaHCO_3$.

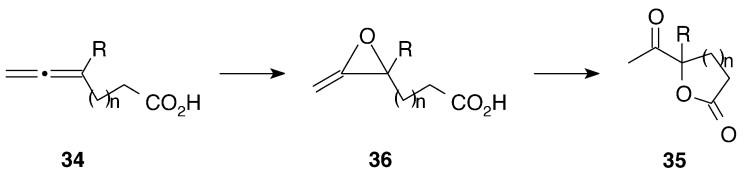
3,4-Hexadienoic acid (**20b**) similarly generated a 2:3 diasteriomeric mixture of *cis* and *trans* hydroxy lactones **21b** in 76% yield upon reaction with DMDO. An in situ oxidation gave only the simple δ-lactone **22b** albeit in a rather mediocre isolated 42% yield and then only if the pH was carefully controlled to avoid decomposition of the starting material. While this result might be construed as an indication that only the remote double bond of **20b** had been epoxidized, this is certainly not consistent with the usual lack of regioselectivity in the epoxidation of 1,3-disubstituted allenes. The low isolated yield in this case leaves open the possibility that some of the unobserved β-lactone **23b** was actually formed in this reaction, but that this species selectively decomposed to uncharacterized products under the reaction conditions. On the other hand, it should be noted that β-lactones have so far only been observed from acids bearing *gem*-dimethyl groups at the 2-position. Whether this influence is operative in promoting cyclization or in retarding further transformations of the strained β-lactones is not clear.

Several allenic acids with longer carbon-chains separating the two functional units were also explored in order to further define the scope of the oxidative cyclization reaction (Scheme 5). The *gem*-dimethyl substituted 4,5-dienoic acid **28a** gave hydroxy γ-lactone **29a** via the intermediate spirodioxide **30a** in good yield upon DMDO oxidation as the free acid (82% yield), with DMDO in the presence of cesium carbonate (100% yield), or even by the in situ procedure (81% yield). The regiochemical course of the lactonization process is completely reversed in this situation. Epoxidation with this substitution pattern should preferentially generate allene epoxide **31a**. However, for the first time under in situ conditions, cyclization of the allene oxide intermediate **31a** is not competitive with further epoxidation, owing no doubt to the remoteness of the two potential reaction centers that greatly slows down this process kinetically. However, once a second epoxidation has occurred to give spirodioxide **30a**, a geometrically more favorable nucleophilic displacement can take place at the internal carbon center of the reactive moiety, which, furthermore, has no other important reaction pathway available to it. Not surprisingly, cyclization occurs via a five-center array to give the observed hydroxy γ-lactone



a, n=1; **b**, n=2; **c**, n=3

Scheme 5.



Scheme 6.

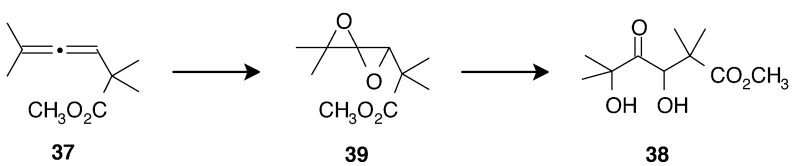
29a. There was no evidence for the other regiochemical mode of cyclization to produce a seven-membered lactone in this instance.

The homologous 5,6-dienoic acid **28b** with the same substitution pattern behaved in a similar manner to generate the analogous hydroxy δ-lactone **29b**, either with DMDO alone (71% yield) or in the presence of Cs_2CO_3 (68% yield). However, extension of the chain by an additional carbon in 6,7-dienoic acid **28c** did not result in cyclization upon DMDO oxidation, but rather gave a mixture from which enone **32** and oxetanone **33** were isolated after treatment with diazomethane. These rearranged materials are the typical acid-catalyzed products expected from isomerization of a simple trisubstituted spirodioxide of this type.[9] The corresponding acids were present in the crude reaction mixture. Obviously, cyclization to a seven-member lactone cannot compete with the acid-catalyzed decomposition of spirodioxide **30b** under these conditions.

A different outcome was demonstrated with the unsubstituted 4,5-hexadienoic acid (**34a**), which reacted with DMDO to give the simple γ-lactone **35a** as the only important isolated product, albeit in a very low 18% isolated yield (Scheme 6). Other major products were not observed here, but might have been lost because of their high polarity. The homologous 5,6-heptadienoic acid (**34b**) gave the corresponding δ-lactone **35b** in a better 68% yield with DMDO in the presence of Cs_2CO_3. Interestingly, the unsymmetrically disubstituted 6,7-dienoic acid **34c**, bearing an additional methyl group at the internal carbon of the allene, was smoothly converted by DMDO in the presence of K_2CO_3 to the seven-membered ε-lactone **35c** in 61% yield. The substitution pattern of allenic acids **34** is the determining factor in this series. The lack of substitution at the allene terminus results in the epoxidation at the internal double bond to give allene oxides **36** as intermediates on the way to the simple five to seven-ring lactones **35**. A geometrically favorable intramolecular nucleophilic attack on the allene oxide unit of intermediates **36** is the predominant reaction pathway here, especially with the more reactive carboxylate anions. Thus, once again there is a clear preference for cyclization over further epoxidation to a spirodioxide with these terminal allenic acids as was observed with allenic acid **12**.

Finally, the observation of participation of appended carbonyl groups of aldehydes and ketones in the ring-opening of allene oxide and spirodioxide intermediates during the epoxidation of allenic derivatives,[17] prompted an examination of the DMDO oxidation of 3,4-dienoate ester **37**, since an analogous process involving the ester function would generate cyclic intermediates that could, in principle, lead to lactone products.[18] Reaction of **37** with DMDO in the presence of molecular sieves produced the acyclic dihydroxy ketone **38** in 80% yield (Scheme 7). An in situ reaction gave a very similar result (69% yield of **38**). Ketone **38** is the hydrolysis product of spirodioxide **39**, which is formed even when only traces of water are present, as in the first experiment. On the basis of earlier studies,[9] a simple spirodioxide with this alkyl substitution pattern should have been stable enough to isolate, so it is quite possible that hydrolysis of spirodioxide **39** is somehow facilitated by nucleophilic participation of the neighboring ester function. In any event, the exclusive formation of acyclic products in this favorable case suggests that allenic esters are not promising as alternate starting materials to the corresponding acids for the synthesis of lactones.

In summary, the DMDO oxidation of a variety of allenic acids has been shown to provide highly functionalized lactones with a range of structural parameters. These transformations proceed via unisolated allene oxides and spirodioxides as intermediates. The exact nature of the product(s) depends on a number of parameters which control the product-determining intermediates and the mode of their further transformations. The structure of the reactant, particularly the substitution pattern, is important in controlling the site of the initial epoxidation and the propensity for a second epoxidation relative to competitive cyclizations by intramolecular attack by the acid function. More substituted allenes typically undergo sequential epoxidation prior to lactone formation, whereas terminal allenes tend to react at the allene oxide stage. The lactonization regiochemistry is usually determined by the relative location of the allene and acid groups in the starting material and shows a decided preference for the formation of normal-sized rings when reacting via the spirodioxides. The reaction conditions can also be critical to the course of the reaction. In general, most oxidations of the free acids proceed via spirodioxides using pre-prepared solutions of



Scheme 7.

DMDO. On the other hand, the in situ method typically involves cyclization at the allene oxide stage. Oxidation of carboxylate anions with DMDO usually gave mixtures of lactones derived from both types of reactive intermediates, but in several cases these conditions resulted in strained β-lactones. At this stage, reasonable predictions can be made on the course of oxidative cyclizations of allenic acids.

3. Experimental

3.1. General procedures

All nuclear magnetic resonance (NMR) spectra were obtained on $CDCl_3$ solutions unless otherwise noted. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer at 400 and 100 MHz or a Bruker AM-500 spectrometer at 500 and 125 MHz, respectively. Infrared (IR) spectra were obtained with a Perkin-Elmer 298 IR spectrometer or a Mattson 4020 Galaxy Series FT-IR. Samples were prepared as thin films on NaCl plates. Mass spectra (HRMS) were obtained on a Kratos MS 80 RFAQQ spectrometer using either chemical (CI) or electron-impact (EI) ionization. Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected.

Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Dichloromethane (CH_2Cl_2) was distilled over calcium hydride under nitrogen. 2,6-Lutidine was distilled from potassium hydroxide and stored over molecular sieves. *t*-Butyldimethylsilyl triflate (TBDMSOTf) was distilled before use. Reagent grade acetone was used in the preparation of dimethyldioxirane (DMDO). High Pressure Liquid Chromatography (HPLC) was performed on a Rainin HPLC using a Dynamax-60A silica gel column with HPLC grade solvents. Silica gel 60 (230–400 mesh, E. Merck) was used for column chromatography. Preparative thin-layer chromatography was performed on Kieselgel 60 F-254 silica gel on 10×20 cm^2 plates of 0.25 mm thickness.

3.2. General procedure for DMDO oxidations of allenic acids

To 1 equiv. of allenic acid was added an excess (6–10 equiv.) of a cold solution of DMDO[11] in acetone. After 0.5–2 h, the reaction mixture was concentrated and the residue was diluted with methylene chloride, dried ($MgSO_4$), and concentrated. The product was purified by recrystallization, flash chromatography, HPLC, etc.

3.2.1. 3-Hydroxy-5-methyl-4-oxo-5-hexanolide (7a). Reaction of 50 mg of **6a** with 40 ml of DMDO gave 55 mg (87%) of **7a** after recrystallization (hexane) as a white solid: IR 3530–3300, 1753, 1737, 1270, 1130 cm^{-1}; ^1H NMR δ 4.62 (dd, 1, J=14, 7 Hz), 3.30 (dd, 1, J=17, 7 Hz), 2.72 (dd, 1, J=17, 14 Hz), 2.15 (s, 1), 1.58 (s, 3), 1.55 (s, 3); ^{13}C NMR δ 209.2, 166.8, 85.7, 67.6, 36.4, 26.9, 25.9; Anal. calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.73; H, 6.29. Characteristic NMR signals corresponding to a small amount of 2-hydroxy-2-methylpent-4-en-3-one[19] were observed in the crude product.

3.2.2. 3-Hydroxy-2,5-dimethyl-4-oxo-5-hexanolide (7b). Reaction of 75 mg of **6b** with 40 ml of DMDO gave after recrystallization (hexane) 85 mg (92%) of a white solid 3:2 mixture of *cis* and *trans* **7b**: IR 3154, 1722, 1279, 1093 cm^{-1}; HRMS (CI) *m/z* (rel intensity) 173 (87), 155 (100), 137 (36), 116 (43), 114 (14), 86 (35), 71 (19); exact mass 173.0813; calcd for $C_8H_{13}O_4$ 173.0813; *cis* **7b**: ^1H NMR δ 4.84 (dd, 1, J=6.5, 3.5 Hz), 3.37 (qd, 1, J=7.8, 6.5 Hz), 3.32 (d, 1, J=3.5 Hz), 1.60 (s, 3), 1.56 (s, 3), 1.20 (d, 3, J=7.8 Hz); ^{13}C NMR δ 209.2, 170.4, 85.6, 70.4, 41.4, 27.4, 25.7, 11.2; *trans* **7b**: ^1H NMR δ 4.29 (dd, 1, J=13.2, 3.0 Hz), 3.39 (d, 1, J=3.0 Hz), 2.67 (dq, 1, J=13.4, 6.7 Hz), 1.59 (s, 3), 1.56 (s, 3), 1.47 (d, 3, J=6.7 Hz); ^{13}C NMR δ 209.2, 170.2, 85.3, 72.1, 41.0, 26.8, 26.0, 12.7.

To a solution of 77 mg (0.45 mmol) of this mixture and 79 μl (0.68 mmol) of 2,6-lutidine in 5 ml of CH_2Cl_2 at −78°C was added 180 μl of TBDMSOTf. After stirring for 4 h, the solution was diluted with ether, washed with sat. $CuSO_4$ and brine, dried ($MgSO_4$) and concentrated. Flash chromatography (20% ether/hexane) afforded 65 mg (50%) of the TBDMS ether of *trans* **7b**: IR 1742, 1257, 1168, 1121 cm^{-1}; ^1H NMR δ 4.27 (d, 1, J=12 Hz), 2.82 (dq, 1, J=12, 6 Hz), 1.56 (s, 3), 1.51 (s, 3), 1.38 (d, 3, J=6 Hz), 0.93 (s, 9), 0.17 (s, 3), 0.06 (s, 3); ^{13}C NMR δ 207.2, 171.0, 85.5, 73.7, 41.5, 26.9, 26.3, 25.6, 18.5, 13.0; HRMS (CI) *m/z* (rel intensity) 287 (2), 229 (8), 201 (12), 173 (18), 157 (42), 143 (100), 129 (68), 115 (39), 75 (52); exact mass 287.166; calcd for $C_{14}H_{27}O_4$ 287.1678 and 23 mg (34%) of 3,5-dimethyl-4-oxo-5-hex-2-enolide (**11**): IR 1735, 1690, 1623, 1262, 1110 cm^{-1}; ^1H NMR δ 6.58 (s, 1), 2.19 (d, 3, J=1 Hz), 1.58 (s, 6).

3.2.3. 3-Hydroxy-2,2,5-trimethyl-4-oxo-5-hexanolide (7c). Reaction of 100 mg of **6c** with 30 ml of DMDO gave 116 mg (96%) of **7c** as a white solid after recrystallization (hexane), mp 95–96°C; IR 3520, 2980, 1760, 1745, 1120 cm^{-1}; ^1H NMR δ 4.54 (d, 1, J=4 Hz), 3.33 (d, 1, J=4 Hz), 1.62 (s, 3), 1.57 (s, 3), 1.49 (s, 3), 1.08 (s, 3); ^{13}C NMR δ 209.0, 173.1, 85.4, 74.4, 45.2, 27.6, 25.4, 23.6, 19.0; Anal. calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.22; H, 7.63.

3.2.4. 2,2-Dimethyl-4-oxo-3-pentanolide (13). Reaction of 100 mg of **12** with 50 ml of DMDO gave after flash chromatography (20% ether/hexane) 62 mg (52%) of **13** as a white solid: IR 1833, 1728, 1184, 1098 cm^{-1}; ^1H NMR δ 4.54 (s, 1), 2.30 (s, 3), 1.54 (s, 3), 1.23 (s, 3); ^{13}C NMR δ 204.4, 173.1, 82.6, 57.7, 27.7, 22.4, 17.6; HRMS (CI) *m/z* (rel intensity) 143 (11), 117 (11), 114 (23), 99 (30), 85 (35), 83 (100), 72 (52), 70 (28); exact mass 143.070; calcd for $C_7H_{11}O_3$ 143.0708.

3.2.5. 3-Hydroxy-2,2-dimethyl-4-oxo-5-octanolide (21a). Reaction of 100 mg of **20a** with 50 ml of DMDO gave a mixture that was separated by HPLC (30% ethyl acetate/hexane) to give 36 mg (30%) of *trans* **21a** as an oil: IR 3507, 2968, 1751, 1734, 1116 cm^{-1}; ^1H NMR δ 4.81 (ddd, 1, J=6, 3, 1 Hz), 4.42 (d, 1, J=1 Hz), 3.38 (br s, 1), 2.09 (m, 1), 1.62 (m, 3), 1.46 (s, 3), 1.08 (s, 3), 0.97 (t, 3, J=7 Hz); ^{13}C NMR δ 206.1, 173.1, 82.5, 76.1, 44.5, 34.5, 23.3, 19.4, 18.7, 13.4; Anal. calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.11; H, 7.94 and 63 mg (53%) of *cis* **21a** as a white solid,

mp 79–80°C: IR 3511, 2980, 1753, 1736, 1105 cm^{-1}; ^1H NMR δ 4.74 (t, 1, J=6 Hz), 4.33 (s, 1), 3.70 (s, 1), 1.88 (m, 2), 1.52 (m, 2), 1.46 (s, 3), 1.07 (s, 3), 0.95 (t, 3, J=7 Hz); ^{13}C NMR δ 207.7, 173.2, 81.9, 75.8, 44.4, 34.7, 22.8, 17.9, 17.6, 13.5; MS (CI) *m/z* (rel intensity) 201 (11), 183 (3), 144 (5), 83 (6), 72 (100); exact mass 201.113; calcd for $C_{10}H_{16}O_4$ 201.1127.

3.2.6. 3-Hydroxy-4-oxo-5-hexanolide (21b). Reaction of 32 mg of **20b** with 30 ml of DMDO gave 30 mg (76%) of **21b** as a 2:3 mixture of stereoisomers: IR 3510, 1753, 1726 cm^{-1}; HRMS (CI) *m/z* (rel intensity) 145 (100), 144 (10), 129 (8), 127 (54), 109 (40), 101 (10), 88 (62); exact mass 145.048; calcd for $C_6H_9O_4$ 145.0500; One isomer shows: ^1H NMR δ 5.03 (q, 1, J=6 Hz), 4.60 (m, 1), 3.08 (m,1), 2.99 (m, 1), 1.43 (d, 3, J=6 Hz); ^{13}C NMR δ 205.2, 170.9, 79.3, 68.2, 37.5, 16.7. The other isomer shows: ^1H NMR δ 5.03 (q, 1, J=6 Hz), 4.52 (m, 1), 3.22 (m, 1), 2.93 (m, 1), 1.45 (d, 3, J=6 Hz); ^{13}C NMR δ 204.8, 170.7, 79.0, 68.5, 37.0, 17.8. The ^{13}C NMR data was assigned to the two isomers on the basis of a correlation between the proton and carbon data from a HETCOR NMR study.

3.2.7. 6-Hydroxy-6-methyl-5-oxo-4-heptanolide (29a). Reaction of 75 mg of **28a** with 30 ml of DMDO gave after molecular distillation 100 mg (82%) of **29a** as a clear oil: IR 3612, 3508, 1784, 1730, 1157 cm^{-1}; ^1H NMR δ 5.49 (m, 1), 3.06 (br s, 1), 2.53 (m, 3), 2.26 (m, 1), 1.43 (s, 3), 1.42 (s, 3); ^{13}C NMR δ 209.6, 176.6, 77.9, 76.8, 26.8, 26.7, 25.1; HRMS (CI) *m/z* (rel intensity) 173 (78), 155 (46), 113 (11), 95 (41), 85 (27), 69 (11); exact mass 173.082; calcd for $C_8H_{13}O_4$ 173.0814.

3.2.8. 7-Hydroxy-7-methyl-6-oxo-5-octanolide (29b). Reaction of 57 mg of **28b** with 40 ml of DMDO gave after molecular distillation 48 mg (71%) of **29b** as a clear oil: IR 3477, 1742, 1728, 1110 cm^{-1}; ^1H NMR δ 5.53 (t, 1, J=6 Hz), 2.94 (br s, 1), 2.56 (m, 2), 2.16 (m, 2), 1.87 (m, 2), 1.43 (s, 3),1.41 (s, 3); ^{13}C NMR δ 210.0, 170.2, 79.5, 77.2, 29.5, 27.1, 26.9, 24.1, 17.2; Anal. calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.99; H, 7.42.

3.2.9. Oxidation of 8-methyl-6,7-nonadienoic acid (28c) with DMDO. Reaction of 132 mg of **28c** and 35 ml of DMDO gave a crude product that was dissolved in 10 ml of methanol and treated with an ethereal solution of diazomethane until the yellow color persisted. Flash chromatography (40% ether/hexane) gave 42 mg (25%) of *8-carbomethoxy-4-hydroxy-2-methylocta-1-en-3-one* ***(32)*** as an oil: IR 3410, 3105, 1734, 1671, 1631, 1215 cm^{-1}; ^1H NMR (δ 5.91 (m, 2), 4.80 (br s, 1), 3.66 (s, 3), 3.47 (s, 1), 2.30 (t, 2, J=7 Hz), 1.93 (dd, 3, J=2, 1 Hz), 1.81 (m, 2), 1.65 (m, 2), 1.50 (m, 2) and 24 mg (14%) of *4-(4-carbomethoxybutyl)-2,2-dimethyl-3-oxacyclobutanone* ***(33)*** as an oil: IR 1816, 1734, 1215 cm^{-1}; ^1H NMR δ 5.28 (t, 1, J=7 Hz), 3.66 (s, 3), 2.32 (t, 2, J=7 Hz), 1.81 (m, 2), 1.66 (m, 2), 1.50 (m, 2), 1.47 (s, 3), 1.45 (s, 3).

3.2.10. 5-Oxo-4-hexanolide (35a).[20] Reaction of 50 mg of **34a** with 30 ml of DMDO gave 10 mg (18%) of **35a** as an oil: IR 1785, 1718 cm^{-1}; ^1H NMR δ 4.81 (m, 1), 2.54 (m, 3), 2.30 (m, 2), 2.25 (m, 2).

3.2.11. Methyl 3,5-dihydroxy-2,2,5-trimethyl-4-oxo-hexanoate (38). Reaction of 50 mg of **37** and 55 ml of DMDO in the presence of 1 g of powdered 3 Å molecular sieves gave after flash chromatography (10% EtOAc/hexane) 52 mg (80%) of **38** as an oil: IR 3464, 1721, 1153, 1047 cm^{-1}; ^1H NMR δ 4.43 (br s, 1), 3.37 (s, 3), 3.58 (br s, 1), 1.40 (s, 3), 1.38 (s, 3), 1.30 (s, 3), 1.18 (s, 3); ^{13}C NMR δ 212.4, 178.0, 78.3, 77.8, 52.3, 27.4, 26.3, 22.5, 22.2; HRMS (CI) *m/z* (rel intensity) 219 (6), 187 (12), 169 (18), 132 (41), 114 (89), 99 (37), 83 (66), 71 (31), 59 (73), 48 (100); exact mass 219.122; calcd for $C_{10}H_{19}O_5$ 219.1232

3.3. DMDO oxidations in the presence of carbonate

The oxidations were performed in a manner similar to the other DMDO reactions except that the acids were stirred with $NaHCO_3$ (0.5 g), K_2CO_3 (1.5 equiv.), or Cs_2CO_3 (1 equiv.) in 1–5 ml of acetone prior to the addition of DMDO.

3.3.1. Oxidation of 6a in the presence of $NaHCO_3$. From 100 mg of **6a** was obtained after flash chromatography (20% ethyl acetate/hexane) 6 mg (10%) of **10a** and 33 mg (52%) of **7a**.

3.3.2. Oxidation of 6b in the presence of $NaHCO_3$. From 100 mg of **6b** was obtained after flash chromatography (10% ethyl acetate/hexane) 31 mg (28%) of **10b** and 66 mg (54%) of a 3:2 mixture of *cis* and *trans* **7b**.

3.3.3. Oxidation of 6c in the presence of $NaHCO_3$. From 300 mg of **6c** was obtained after flash chromatography 159 mg (44%) of **7c**, 37 mg (11%) of **10c**, and 41 mg (11%) of *5-hydroxy-2,2,5-trimethyl-4-oxo-3-hexanolide* ***(19)*** as a white solid, mp 92–93°C: IR 3620, 2984, 1840, 1740, 1100 cm^{-1}; ^1H NMR δ 5.18 (s, 1), 2.24 (s, 1), 1.55 (s, 3), 1.42 (s, 3), 1.41 (s, 3), 1.23 (s, 3); ^{13}C NMR δ 207.5, 173.2, 81.2, 77.1, 58.6, 27.6, 25.9, 21.7, 18.1; Anal. calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.99; H, 7.63.

3.3.4. Oxidation of 12 in the presence of $NaHCO_3$. Reaction of 100 mg of **12** gave after flash chromatography (20% ether/hexane) 100 mg (84%) of **13**.

3.3.5. Oxidation of 20a in the presence of $NaHCO_3$. Reaction of 100 mg of **20a** gave after flash chromatography (50% ether/pentane) 8 mg (7%) of **22a**, 10 mg (9%) of **23**, 44 mg (37%) of **21a** as a 2:3 mixture of *cis* and *trans* isomers and 12 mg (10%) of a 2:1 mixture of diastereomers of *5-hydroxy-2,2-dimethyl-4-oxo-3-pentanolide* ***(26)*** as a clear oil: IR 3522, 1835, 1724 cm^{-1}; ^1H NMR δ 4.65 (m, 2), 4.11 (m, 1, J=7, 2 Hz), 4.04 (m, 1), 2.33 (d, 1, J=3 Hz), 1.75 (d, 1, J=3 Hz), 1.74–1.32 (m, 4), 1.32–1.31 (four overlapping singlets, **12**), 0.98 (t, 3, J=7 Hz), 0.96 (t, 3, J=7 Hz); ^{13}C NMR δ 212.0, 211.1, 178.0, 85.3, 71.7, 70.7, 44.7, 44.2, 35.6, 33.7, 22.0, 21.8, 19.4, 19.2, 18.9, 18.6, 13.7, 13.6; HRMS (CI) *m/z* (rel intensity) 201 (16), 183 (9), 155 (7), 128 (46), 113 (6), 100 (100), 73 (30), 70 (33), 55 (64), 41 (27); exact mass 201.112; calcd for $C_{10}H_{17}O_4$ 201.1126.

3.3.6. Oxidation of 28a in the presence of Cs_2CO_3. Reaction of 26 mg of **28a** gave 32 mg (100%) of **29a**.

3.3.7. Oxidation of 28b in the presence of Cs_2CO_3. Reaction of 57 mg of **28b** gave after molecular distillation 25 mg (83%) of **29b**.

3.3.8. 6-Oxo-5-heptanolide (35b). Reaction of 94 mg of K_2CO_3 and 57 mg of **34b** gave after preparative TLC (ether) 45 mg (68%) of **35b** as an oil: IR 1727, 1716, 1286, 1172, 1091, 1020 cm^{-1}; ^1H NMR δ 4.75 (t, 1, J=6 Hz), 2.60 (m, 2), 2.31 (s, 3), 2.15 (m, 1), 1.89 (m, 3); ^{13}C NMR δ 206.4, 173.1, 80.5, 38.2, 30.6, 27.1, 26.9; HRMS (CI) m/z (rel intensity) 143 (20), 99 (100), 84 (26), 71 (89), 55 (81); exact mass 143.069; calcd for $C_7H_{11}O_3$ 143.0708.

3.3.9. 6-Methyl-7-oxo-6-octanolide (35c). Reaction of 166 mg of K_2CO_3 and 148 mg of **34c** gave 100 mg (61%) of **35c** as an oil: IR 2942, 1728, 1715, 1172, 1091, 1020, 913 cm^{-1}; ^1H NMR δ 2.72 (m, 1), 2.37 (m, 1), 2.26 (m, 2), 2.25 (s, 3), 1.85 (m, 1), 1.74 (m, 1), 1.61 (m, 2), 1.50 (s, 3); ^{13}C NMR δ 207.4, 174.0, 87.8, 36.7, 36.6, 26.9, 25.0, 24.8, 22.5; Anal. calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.20; H, 7.98.

3.4. In situ oxidations

To a mixture of the allenic acid, 8 g (96 mmol) of sodium bicarbonate, 20 ml of acetone, 10 ml of methylene chloride and 60 ml of water was slowly added 100 g (160 mmol) of Oxone with vigorous stirring. After 2 h, the mixture was filtered through Celite and the filtrate was extracted with ether. The extracts were dried ($MgSO_4$), concentrated and purified.

3.4.1. 5-Methyl-4-oxo-5-hexanolide (10a). Reaction of 160 mg of **6a** gave after flash chromatography (25% ethyl acetate/hexane) 110 mg (67%) of **10a** as an oil: IR 1733, 1727, 1130 cm^{-1}; ^1H NMR δ 2.90 (m, 2), 2.75 (m, 2), 1.52 (s, 3), 1.51 (s, 3); ^{13}C NMR δ 207.3, 169.1, 86.4, 33.3, 28.4, 25.9; HRMS (CI) m/z (rel intensity) 143 (100), 142 (30), 125 (54), 114 (53), 70 (13); exact mass 143.071; calcd for $C_7H_{10}O_3$ 143.0708.

3.4.2. 2,5-Dimethyl-4-oxo-5-hexanolide (10b). Reaction of 200 mg of **6b** gave after recrystallization (hexane) 164 mg ((74%) of **10b** as a white solid, mp 72–75°C: IR 1734, 1726, 1210 cm^{-1}; ^1H NMR δ 2.83 (m, 1), 2.62 (dd, 1, J=17, 5 Hz), 2.55 (dd, 1, J=17, 13 Hz), 1.46 (s, 3), 1.42 (s, 3), 1.26 (d, 3, J=7 Hz); ^{13}C NMR δ 207.8, 172.4, 87.0, 41.0, 33.3, 26.3, 25.5, 16.0; HRMS (CI) m/z (rel intensity) 157 (20), 139 (40), 128 (37), 70 (59), 69 (46), 59 (100); exact mass 157.087; calcd for $C_8H_{13}O_3$ 157.0865.

3.4.3. 2,2,5-Trimethyl-4-oxo-5-hexanolide (10c). Reaction of 480 mg of **6c** gave after recrystallization (hexane) 400 mg (76%) of **10c** as a white solid, mp 94–95°C; IR 2980, 1737, 1726, 1120 cm^{-1}; ^1H NMR δ 2.67 (s, 2), 1.54 (s, 6), 1.32, (s, 6); ^{13}C NMR δ 207.9, 174.4, 87.9, 46.9, 39.6, 26.5, 26.4; Anal. calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.77; H, 8.36.

3.4.4. 2,2-Dimethyl-4-oxo-3-pentanolide (13). Reaction of 200 mg of **12** gave 170 mg (72%) of **13**.

3.4.5. Oxidation of 20a. Reaction of 360 mg of **20a** gave after flash chromatography (25% ether/pentane) 210 mg (53%) of **2,2-dimethyl-4-oxo-5-octanolide (22a)** as a white solid, mp 74–75°C: IR 1747, 1734, 1122 cm^{-1}; ^1H NMR δ 4.70 (dd, 1, J=8, 4 Hz), 2.69 (d, 1, J=16 Hz), 2.51 (d, 1, J=16 Hz), 1.85 (m, 2), 1.50 (m, 2), 1.36 (s, 3), 1.28 (s, 3), 0.94 (t, 3, J=7 Hz); ^{13}C NMR δ 206.3, 174.5, 84.0, 48.3, 38.5, 34.3, 26.4, 24.7, 17.9, 13.6; HRMS (CI) m/z (rel intensity) 185 (97), 167 (18), 156 (29), 142 (50), 128 (25), 83 (24), 71 (100); Anal. calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.22; H, 8.72 and 100 mg (25%) of **2,2-dimethyl-4-oxo-3-octanolide (23)** as a clear oil: IR 1836, 1716, 1096, 913, 747 cm^{-1}; ^1H NMR δ 4.55 (s, 1), 2.57 (sym m, 2), 1.59 (m, 2), 1.54 (s, 3), 1.35 (m, 2), 1.20 (s, 3), 0.92 (t, 3, J=7 Hz).

3.4.6. 4-Oxo-5-hexanolide (21b).[20] This reaction was modified by the addition of 1 g of $NaHCO_3$ after each 7-g portion of Oxone using 200 mg of **20b** to give after flash chromatography (20% ethyl acetate/hexane) 96 mg (42%) of **22a** as a white solid, mp 74–75°C: IR 1730, 1274, 1123, 1072 cm^{-1}; ^1H NMR δ 4.78 (q, 1, J=6 Hz); 2.93 (m, 2), 2.74 (m, 2), 1.51 (d, 3, J=6 Hz); ^{13}C NMR δ 205.4, 170.0, 79.5, 33.2, 28.2, 15.9; HRMS (CI) m/z (rel intensity) 129 (100), 167 (7), 111 (90), 100 (28), 86 (42), 84 (64), 56 (86); exact mass 129.056; calcd for $C_{10}H_{17}O_3$ 129.0552.

3.4.7. 6-Hydroxy-6-methyl-5-oxo-4-heptanolide (29a). Reaction of 200 mg of **28a** gave after flash chromatography (30% ether/hexane) 200 mg (81%) of **29a**.

3.4.8. Methyl 3,5-dihydroxy-2,2,5-trimethyl-4-oxo-hexanoate (38). Reaction of 200 mg of **37** gave after chromatography (30% ethyl acetate/hexane) 160 mg (69%) of **38**.

3.5. Oxidations in the presence of *p*-toluenesulfonic acid

Reactions were performed as usual except that a solution of 1 equiv. of allenic acid in 5–10 ml of methylene chloride was added to a solution of 2 equiv. of *p*-toluenesulfonic acid in 6–10 equiv. of DMDO in acetone.

3.5.1. Oxidation of 6c. Reaction of 50 mg of **6c** gave 53 mg (88%) of a 1:4 mixture of **10c** and **7c**.

3.5.2. Oxidation of 12. Reaction of 100 mg of **12** after pouring into sat. $NaHCO_3$, followed by drying and concentration of the organic layer and flash chromatography (30% ethyl acetate/hexane) of the residue gave 17 mg (15%) of **13**, 68 mg (43%) of **16** as a white solid, mp 50–51°C: IR 1773, 1282, 1223, 1086 cm^{-1}; ^1H NMR δ 4.17 (s, 1), 1.76 (s, 3), 1.45 (s, 3), 1.41 (s, 3), 1.32 (s, 3), 1.30 (s, 3); ^{13}C NMR δ 178.8, 112.8, 110.6, 87.9, 46.1, 27.7, 27.1, 23.9, 23.7, 19.0; HRMS (CI) m/z (rel intensity) 201 (27), 185 (42), 143 (38), 115 (41), 98 (60), 83 (100); exact mass 201.112; calcd for $C_{10}H_{17}O_4$ 201.1126 and 55 mg (32%) of **17** as a white solid, mp 105–107°C: IR 3620, 3475, 1778, 1218, 1078 cm^{-1}; ^1H NMR δ 4.48 (d, 1, J=10 Hz), 4.14 (d, 1, J=10 Hz), 4.09 (d, 1, J=4 Hz), 2.64 (d, 1, J=4 Hz), 1.52 (s, 3), 1.44 (s, 3), 1.36 (s, 3), 1.19 (s, 3); ^{13}C NMR δ 179.2, 113.2, 111.7, 79.9, 70.3, 44.7, 26.3, 25.9, 23.4, 18.2; HRMS (CI) m/z (rel intensity) 217 (100), 201 (74), 199 (18), 159

(55), 117 (29), 114 (25), 101 (23), 72 (90), 59 (63); exact mass 217.107; calcd for $C_{10}H_{17}O_5$ 217.1075.

3.5.3. 4-Hydroxy-2,2,5-trimethyl-3-oxo-5-hexanolide (19). Silica gel (ca. 2 g) was added to a solution of 50 mg of **7c** in 10 ml of THF until a thick slurry was formed. After 24 h, the mixture was filtered through Celite and concentrated to give a yellow liquid. Preparative TLC (30% ether/pentane) gave 40 mg (80%) of **19**: IR 3750, 2985, 1753, 1738, 1125 cm^{-1}; ^1H NMR δ 4.50 (s, 1), 2.15 (br s,1), 1.41 (s, 3), 1.39 (s, 3), 1.33 (s, 3), 1.32 (s, 3); ^{13}C NMR δ 211.2, 177.7, 88.3, 72.1, 44.4, 26.5, 24.9, 22.2, 19.3; Anal. calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.04; H, 7.65.

3.6. Isomerization of 19 to 7c

3.6.1. Isomerization by K_2CO_3. A mixture of 21 mg of **19** and 20 mg of K_2CO_3 in 20 ml of acetone was stirred for 40 min. Concentration, dilution with CH_2Cl_2, drying ($MgSO_4$), and concentration gave a sample whose ^1H NMR spectrum indicated a 2:1 mixture of lactones **7c** and **19**.

3.6.2. Stability of 19 to acetic acid. To 30 mg of a mixture of lactones **7c** and **19** in an NMR tube was added 5 μl of water, 10 μl of acetic acid and 1 ml of acetone-d_6. After 2 h, the ratio of **7c** and **19** was unchanged by ^1H NMR.

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References

1. (a) Stang, P. J. In *The Chemistry of Functional Groups, Supplement E. The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues*; Patai, S., Ed.; Wiley: New York, 1980; pp 859–879. (b) Chan, T. H.; Ong, B. S. *Tetrahedron* **1980**, *36*, 2269–2289.
2. Crandall, J. K.; Machleder, W. H. *Tetrahedron Lett.* **1966**, 6037–6041.
3. Crandall, J. K.; Machleder, W. H.; Sojka, S. A. *J. Org. Chem.* **1973**, *38*, 1149–1154.
4. Camp, R. L.; Greene, F. D. *J. Am. Chem. Soc.* **1968**, *90*, 7349.
5. Crandall, J. K.; Conover, W. W.; Komin, J. B.; Machleder, W. H. *J. Org. Chem.* **1974**, *39*, 1723–1729.
6. Crandall, J. K.; Machleder, W. H. *J. Am. Chem. Soc.* **1968**, *90*, 7347–7349.
7. Crandall, J. K.; Machleder, W. H.; Thomas, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 7346–7347.
8. Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847–2853.
9. Crandall, J. K.; Batal, D. J.; Sebesta, D. P.; Lin, F. *J. Org. Chem.* **1991**, *56*, 1153–1166.
10. (a) Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311–3314. (b) Baumstark, A. L.; Vasquez, P. C. *J. Org. Chem.* **1988**, *53*, 3437–3439.
11. Crandall, J. K.; Batal, D. J.; Lin, F.; Reix, T.; Nadol, G. S.; Ng, R. A. *Tetrahedron* **1992**, *48*, 1427–1448.
12. Bertrand, M.; Dulcere, J. P.; Gil, G. *Tetrahedron Lett.* **1980**, *21*, 1945–1948. Bertrand, M.; Dulcere, J. P.; Gil, G. *Tetrahedron Lett.* **1977**, *18*, 3807–3810. Bertrand, M.; Dulcere, J. P.; Gil, G.; Grimaldi, J.; Sylvestre-Panthet, P. *Tetrahedron Lett.* **1976**, *17*, 3305–3308.
13. For a preliminary publication, see: Crandall, J. K.; Rambo, E. *J. Org. Chem.* **1990**, *55*, 5929–5930.
14. *PCMODEL v7.5*; Serena Software, Box 3076, Bloomington, IN 47402-3076.
15. Crandall, J. K.; Reix, T. *Tetrahedron Lett.* **1994**, *35*, 2513–2516.
16. Kirby, A. *J. Adv. Phys. Org. Chem.* **1980**, *17*, 183–278.
17. Crandall, J. K.; Rambo, E. *Tetrahedron Lett.* **1994**, *35*, 1489–1492.
18. Kolsaker, P.; Boerresen, S. *Acta Chem. Scand., Ser.* **1979**, *B33*, 133–137.
19. Hoff, S.; Brandsma, L.; Arens, J. F. *Rec. Trav. Chim.* **1968**, *87*, 159–161.
20. Jensen, J. E.; Torssell, K. *Acta Chem. Scand., Ser.* **1978**, *B32*, 457–459.