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Ozonolysis of Bicyclic 1,2-Dioxines: Initial Scope and Mechanistic Insights

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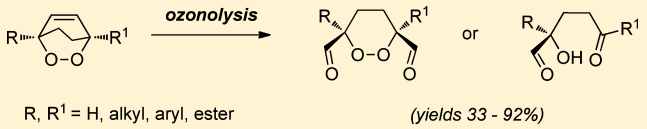
Supporting Information

ABSTRACT: The ozonolysis of bicyclic 1,2-dioxines was investigated using a variety of 1,4-disubstituted 1,2-dioxines along with a 1,3-dialkyl and steroidal example, with yields ranging from moderate to excellent. Two different pathways were observed upon reaction of the 1,4-disubstituted 1,2-dioxines with ozone; one pathway saw the "expected" results, that is, cleavage of the olefinic moiety with generation of 1,4-dicarbonyl 1,2-dioxines, while the other pathway revealed a previously unobserved rearrangement involving cleavage of the peroxide linkage along with loss of either CO or CO_2. Several unsymmetrical ozonolyses were also performed to further investigate the origins of this rearrangement, and initial mechanistic insights into the fragmentation pathways are discussed.



INTRODUCTION

Cyclic peroxides are an important class of organic compounds classified by their weak O−O linkage. They are abundant in nature with many natural products being isolated that exhibit a wide spectrum of biological activities including antimalarial,[1] antifungal[2,3] and cytotoxic activities against cancer cells.[4] 1,2-Dioxines, also known as endoperoxides, are a specific type of cyclic peroxide, characterized by an unsaturated six-membered peroxide ring. Synthetically, they have proven to be extremely versatile starting materials with extensive research highlighting numerous examples whereby the peroxide bond is either cleaved[5−12] or maintained[12−18] during the course of further reaction. Continuing our studies into the chemistry of 1,2-dioxines, we have now turned our attention to the products that result, and the possible synthetic utility generated, from the ozonolysis of 1,2-dioxines.

The ozonolysis of alkenes, first reported in 1840, remains one of the most important and classical methods for oxidative cleavage of alkenes.[19] Since the basic mechanism was formulated by Criegee in the mid-1950s,[20,21] a large amount of work has been done on the mechanism, although not all details are fully understood.[22−25] While the Criegee mechanism has become generally accepted, a number of exceptions to this mechanism have appeared, prompting numerous "modified-Criegee" mechanisms to be reported.[26−28] Decomposition of the ozonides that result from this reaction can be carried out using a variety of different reagents, to furnish a number of functional products, with triphenylphosphine (PPh_3) being a widespread reagent for their reduction resulting in the formation of dicarbonyl products.[29,30] Despite all this attention, little precedent exists for the ozonolysis of bicyclic or other polycyclic alkenes,[31−33] and to the best of our knowledge, only two examples can be found within the literature involving the ozonolysis of alkene systems incorporating the 1,2-dioxine functionality. The natural product (−)-Warburganal (**3**) was synthesized in 15 steps from levopimaric acid in an overall yield of 2.7%.[34] This synthesis involved the ozonolysis of bicyclic 1,2-dioxine **1** to furnish keto-aldehyde **2** (Scheme 1), in a near quantitative crude yield, although this paper's discussion placed little emphasis on either the reaction or details of the stability or characterization of the resulting dicarbonyl product.

The other example of interest involved work done some 30 years ago to investigate the ozonolysis of 7-dehydrocholesterol acetate endoperoxide (**4**).[35,36] Ozonolysis was performed on the named steroid in a bid to understand the reaction mechanism and pathways undertaken to the final products, Scheme 2. The resulting ozonide was not reduced but rather allowed to decompose over time with various decomposition products being isolated and characterized along the way. A full transformation into the final products, **5** and **6**, reportedly took approximately eight weeks at ambient temperature, with dialdehyde **7** being isolated as an unstable intermediate. Unfortunately, due to the reported vague reaction conditions along with the insufficient characterization of the products, the only, but important, conclusion that can be drawn from their findings is that ozonolysis of bicyclic 1,2-dioxines appears to proceed with no disruption of the peroxide linkage and dicarbonyl products are formed in the first instance.

Given this clear dearth in the literature concerning the reactivity of bicyclic 1,2-dioxines toward ozone we decided to explore this reaction on a variety of substrates in order to investigate both the synthetic scope and probe the mechanism further. Thus, given our knowledge on the reactivity of 1,2-dioxines coupled with the two examples above, we propose herein that reaction of 1,2-dioxines of the type **8** would consume one mole equivalent of ozone to afford primary ozonide (molozonide) **9**. This would then collapse to ozonide

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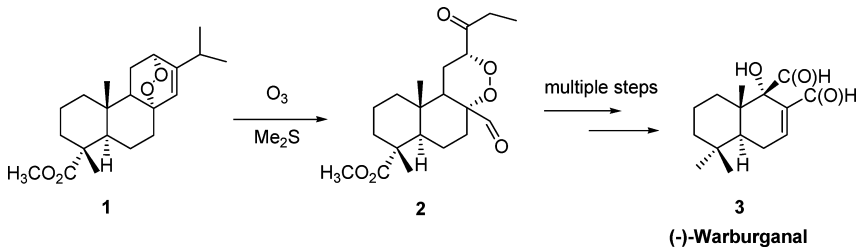
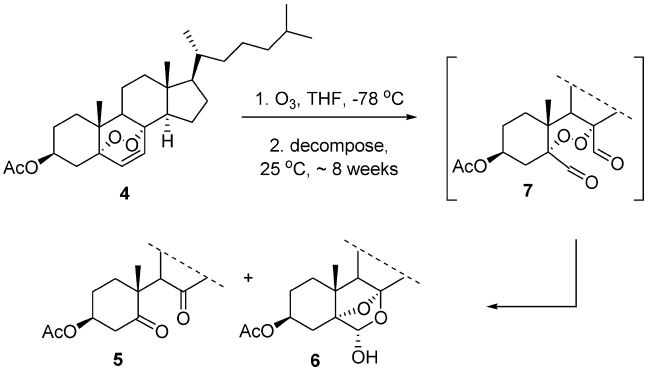
Scheme 1

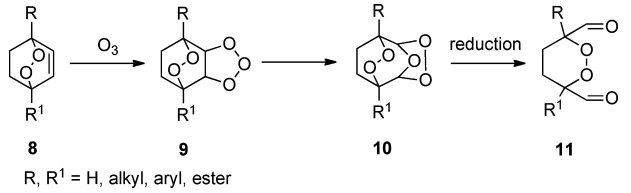


Scheme 2



10 with reductive workup affording dialdehyde **11**, but importantly keeping the peroxide linkage intact, Scheme 3. A

Scheme 3



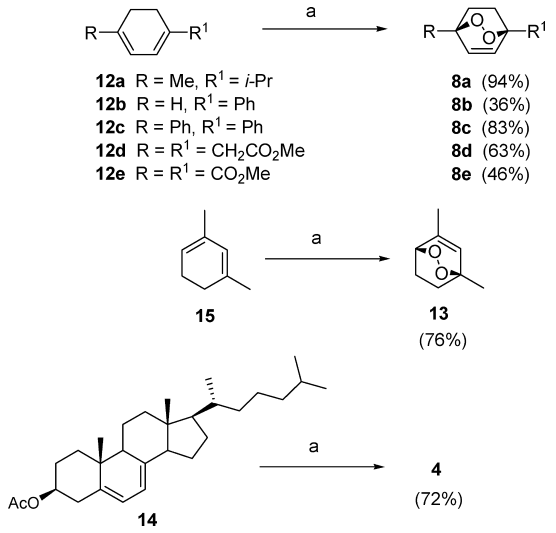
range of simple 1,4-disubstituted bicyclic 1,2-dioxines were chosen for this study, along with a 1,3-dialkyl example containing a substituent directly on the C−C double bond, and a full re-examination of steroid **4** to probe the scope and possible mechanistic outcomes resulting from the ozonolysis of bicyclic 1,2-dioxines.

RESULTS AND DISCUSSION

Synthesis of Bicyclic 1,2-Dioxines (4, 8a−e and 13). All 1,2-dioxines were synthesized via the rose bengal *bis* (triethylammonium) salt sensitized [4π +2π] cycloaddition of their respective cyclic 1,3-hexadienes with singlet oxygen, Scheme 4.[8,37] The 1,4-disubstituted bicyclic 1,2-dioxines **8a−e**, the 1,3-dialkyl substituted analogue **13** and steroid **4** would allow for exploration into the effects of differing substitution patterns, steric and electronic factors on the proposed ozonolysis reaction highlighted within Scheme 3. The synthesis of all requisite bicyclic 1,2-dioxines proceeded smoothly with purified yields ranging from average to excellent, Scheme 4.

Ozonolysis of Bicyclic 1,2-Dioxines (4, 8a−e and 13). All standard ozonolysis reactions were carried out in dichloromethane at −78 °C under an atmosphere of argon. Ozone was generated from oxygen using corona discharge via an ozone generator, and bubbled through the solution as a gaseous

Scheme 4



[a]O_2, DCM, *hv*, rose bengal.

mixture of O_2/O_3. Reactions were continued until the solution turned pale blue, indicating saturation with ozone and cessation of reaction. After completion, the mixture was raised to room temperature, and reduced with PPh_3 (typically 1.1 equiv), unless otherwise stated. For ease of discussion, the results for these ozonolyses have been divided into two categories: first the substrates that behaved as 'expected' toward ozone, and second the substrates that behaved in an "unexpected" manner toward ozone.

1,2-Dioxines that Behaved as "Expected" Toward Ozone. Ozonolysis was initially performed on steroid **4** in order to expand upon the work previously published[35,36] and apply a more rigorous scientific approach toward this reaction by immediately reducing the ozonide upon formation in order to validate that the expected dialdehyde was indeed formed, and to confirm that the peroxide bond was not broken during the process. We found that ozonolysis of dioxine **4** followed by immediate PPh_3 reduction furnished dialdehyde **7** in excellent yield (92%), although product instability was an issue, Scheme 5.

It is known that the peroxide bond of 1,2-dioxines can be readily cleaved upon treatment with an excess of $LiAlH_4$, to furnish the respective diol,[38,39] although in contrast to this, there are also reports detailing the successful use of $LiAlH_4$ to reduce carbonyl functionalities in the presence of peroxide bonds without their rupture.[40] Thus, upon using an excess of $LiAlH_4$ (3 equiv) at 0 °C, dialdehyde **7** was successfully reduced to triol **16**, thus further confirming the presence of the aldehyde moieties within **7**, along with the peroxide bond remaining intact. Previous NMR and computational studies, along with a

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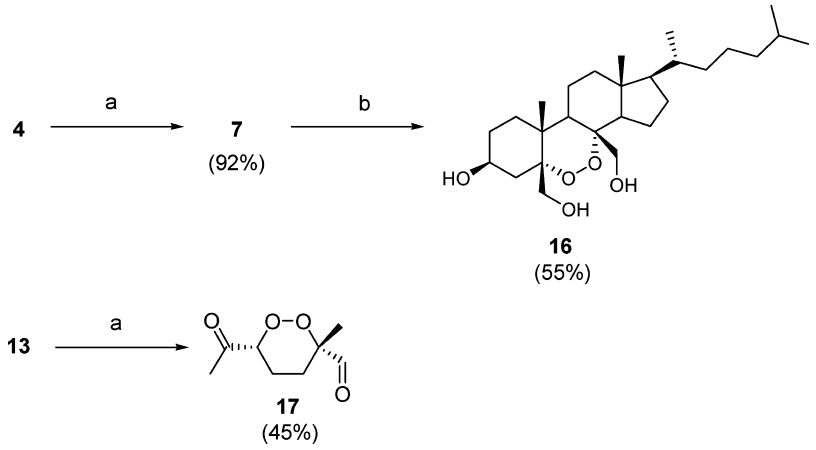
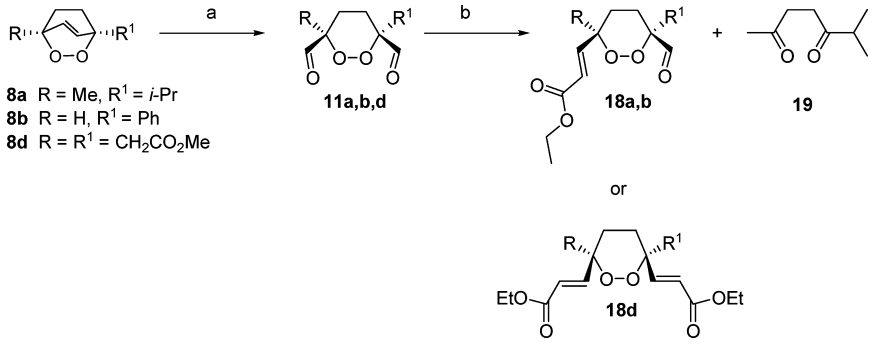
Scheme 5



[a]1. O_3, DCM, −78 °C, 2. PPh_3 (1.1 equiv). [b]$LiAlH_4$ (3 equiv), THF, 0 °C.

Scheme 6



[a]1. O_3, DCM, −78 °C, 2. PPh_3 (1.1 equiv). [b]$Ph_3P{=}CHCO_2Et$ (2 equiv), DCM.

crystal structure, have confirmed that the peroxide bond of **4** is facing in a fixed downward position.[41,42] Upon cleavage of the alkene bond by ozone, the resulting dialdehyde must therefore assume the stereochemistry as shown in Scheme 5, and this relative and absolute stereochemistry must also be that for the triol **16**. The successful formation of **16** clearly confirms that the ozonolysis of bicyclic 1,2-dioxine **4** proceeds via molozonide **9** and ozonide **10** as summarized in Scheme 3 and highlights the potential synthetic utility of this process.

The ozonolysis and subsequent PPh_3 reduction of the 1,3-dimethyl susbsituted 1,2-dioxine **13** also proceeded smoothly, resulting in the desired keto-aldehyde **17** in average yield (45%), Scheme 5. The product was stable upon purification with the aldehyde peak at δ = 9.75 ppm in the ^{1}H NMR spectrum showing a small long-range coupling constant of J = 1.8 Hz. The ROESY spectrum showed a correlation between the aldehyde proton and its peri-methyl protons, which accounts for this long-range coupling. Again, "attack" of ozone on the alkene moiety of the precursor bicyclic 1,2-dioxine **13** dictates that the newly formed ketone and aldehyde functionalities attain the *cis* stereochemistry as shown in Scheme 5.

Ozonolysis and subsequent PPh_3 reduction of dioxines **8a**, **8b** and **8d** also furnished the expected dialdehydes **11a**, **11b** and **11d** in good to average yields with the peroxide bond remaining intact during the course of reaction, Scheme 6. It is also interesting to note the formation of diketone **19** (*vide infra*), appeared in small quantities (ca. 15%) as a byproduct in the reaction mixture for the ozonolysis of 1,2-dioxine **8a**. Product instability did not allow for full characterization, although careful column chromatography provided enough pure sample to characterize dialdehydes **11a** and **11b** by ^{1}H and ^{13}C NMR. Attempts to purify diester dialdehyde **11d** were unsuccessful, with the product appearing to decompose upon exposure to silica, although the crude ^{1}H NMR spectrum showed the presence of two aldehyde peaks, indicating that ozonolysis had been successful. The crude dialdehyde products for **11a**, **11b** and **11d** were therefore subjected to a Wittig reaction using an ethyl ester stabilized phosphorus ylide to form the more stable alkene products (**18a**, **18b** and **18d**) to allow for the full characterization of the sensitive dialdehydes.

Interestingly, the ylide only added to one aldehyde moiety of **11a** and **11b**, determined by 2D NMR to be the least hindered side of each molecule, yielding **18a** and **18b**. Even though this left one aldehyde unprotected, both compounds were sufficiently stable to allow for full characterization, confirming peroxides (**18a** and **18b**), which in turn confirmed the presence of the preceding dialdehydes (**11a** and **11b**). The ylide added to both aldehydes of the diester dialdehyde **11d**, giving the tetra-ester **18d**. Standard proton and carbon NMR spectra of the tetra-ester **18d** acquired at ambient temperature showed broadened peaks, which sharpened upon raising the temperature to +50 °C. Table 1 summarizes the reaction yields over the three steps from dioxines **8a**, **8b** and **8d** to alkenes **18a**, **18b** and **18d** respectively. The ^{1}H NMR spectrum of **11b** showed splitting of J = 1.5 Hz of one of the aldehyde peaks, with similar

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Table 1. Yields for Ozonolysis and Wittig Reactions on 1,2-Dioxines 8a,b and d

dioxine	dialdehyde	yield (%)	alkene	yield (%)[a]
8a	**11a**	77[b]	**18a**	44
8b	**11b**	33[c]	**18b**	10
8d	**11d**	64[b]	**18d**	21

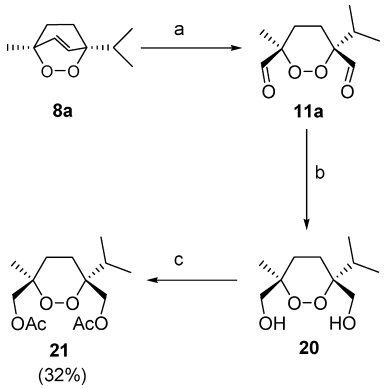
[a]Over three-steps from dioxine to alkene. [b]Estimated, based on the amount of crude reaction material remaining after column chromatography in order to remove the PPh_3O byproduct. [c]Isolated pure sample.

splitting seen again in the ^1H NMR spectra for the protected adduct **18b** (doublet at δ = 9.71 ppm, J = 2.1 Hz), indicative of long-range coupling between the aldehyde and methylene protons.

Although the yields obtained for the formation of alkenes **18a**, **18b** and **18d** appear low to moderate, one must bear in mind that this is the total yield for a three-step process (ozonolysis, reduction and Wittig). It is also worth bearing in mind the complexity of this procedure and the highly reactive intermediates formed upon reacting 1,2-dioxines with ozone. The highly oxygenated primary ozonides (molozonides) and final ozonides are packed with a high density of oxygen atoms with numerous unfavorable lone-pair repulsions possible. These sensitive intermediates would have ample opportunity for cleavage of the weak O−O linkages followed by downstream decomposition, thereby contributing to a lowered overall yield. With these possible constraints in hand, we therefore consider the overall yields obtained for the substrates to be reasonable.

It was decided to also attempt a hydride reduction as an alternative "trapping" technique for the unstable 1,2-dioxine aldehyde **11a**, as this proved successful for the steroid dialdehyde **7**. Ozonolysis was performed on dioxine **8a** to afford the crude dialdehyde **11a**, which was triturated with hexane to remove most of the PPh_3O and subsequently treated with 3 equiv of $LiAlH_4$. The crude mixture containing diol **20** proved difficult to purify thus acetylation was employed to furnish diacetate **21** in 32% yield (over four steps from the dioxine), Scheme 7. Broadened peaks were observed in the ^1H and ^{13}C NMR spectra of the diacetate **21** upon acquisition at ambient temperature. Upon lowering the temperature to −50 °C all the signals separated out into multiple peaks, likely due to "freezing" out the conformers by lowering the interconversion rate. Increasing the temperature to +50 °C saw a single set of sharp peaks, allowing **21** to be fully characterized.

Scheme 7



[a]1. O_3, DCM, −78 °C, 2. PPh_3 (1.1 equiv). [b]$LiAlH_4$ (3 equiv) 0 °C. [c]Ac_2O, DMAP, pyridine.

1,2-Dioxines that Behaved "Unexpectedly" Toward Ozone. The ozonolysis of 1,2-dioxines **8c** and **8e** did not follow the same pathway as the other dioxines mentioned (i.e., to yield the "expected" dialdehydes **11c** and **11e**), and the outcomes of these two reactions are individually discussed below.

Ozonolysis of the diphenyl substituted dioxine **8c** resulted in the formation (*vide infra*) of keto-aldehyde **22** (26%) as a crystalline solid (Scheme 8), with single crystal X-ray analysis unambiguously confirming the structure and stereochemistry. Along with the keto-aldehyde **22**, two other products were isolated, namely terphenyl (**23**) (21%) and the diphenyl diketone **24** (7%). Previously, we saw that the ozonolysis of **8a** resulted in the formation of a similar diketone byproduct, **19a** and their formation will be discussed later. There is no precedent for the formation of terphenyl (**23**) under these circumstances, which raises the question of how and why does **23** form. One possibility is that ozone on interaction with the alkene moiety of **8c** lowers the transition state for cycloreversion aiding the loss of singlet oxygen (to yield diene **12c**) followed by aerial oxidation.

It was considered that dialdehyde **11c** may not have formed due to the presence of the two bulky phenyl groups α to the alkene moiety inhibiting PPh_3 from being able to reduce the ozonide, thereby allowing it to decompose directly into keto-aldehyde **22**. This theory was tested by reducing the ozonolysis products with Me_2S (1.1 equiv) to see whether the same products were formed upon using a smaller reducing agent. Indeed, the same products did form in similar yields and ratios, suggesting the possibility that the combination of the bulkiness of the PPh_3 and phenyl groups of the 1,2-dioxines is not the cause this unusual fragmentation.

Purification of the products formed via the ozonolysis and subsequent reduction of diester dioxine **8e** proved difficult, although the crude ^1H NMR spectrum of the products showed two distinct aldehyde protons as singlets at δ = 9.60 and 9.58 ppm, integrating in a 1:1 ratio. Treatment of this crude mixture with 2 equiv of ethyl ester ylide, resulted in the formation of three products, determined to be **25**, **26** and **27**, totaling 53% yield over the three steps. These three Wittig products appear to have come from "unsymmetrical" keto-aldehyde **28** and "symmetrical" dialdehyde **29** (Scheme 9) in a ratio of approximately 6.5:1 respectively. Symmetrical dialdehyde **29** and its subsequently trapped tetra-ester **27** appear to result from direct cleavage of the peroxide bond during the course of reaction. Structural isomers **25** and **26** occur in an approximately 1:2 ratio, with **25** being the "expected" product upon aldehyde protection of the "unsymmetrical" keto-aldehyde **28** with the ylide, while **26** appears to have undergone alkene migration. Upon subjecting both **25** and **26** to heat and acidic conditions in a bid to facilitate isomerization between the two, no interconversion was observed. Given that five of the bicyclic 1,2-dioxines (**4**, **13**, **8a**, **8b** and **8d**) behaved as expected, affording dicarbonyl products upon ozonolysis, while two dioxines (**8c** and **8e**) deviated from the expected mechanistic outcome, we felt it appropriate the examine the unsymmetrical ozonolysis of bicyclic 1,2-dioxines **8a** and **8e** to probe these mechanistic outcomes further.

Unsymmetrical Ozonolysis of Bicyclic 1,2-Dioxines 8a and 8e. One way to test the mechanistic question of whether these latter two unusual rearrangements were occurring via

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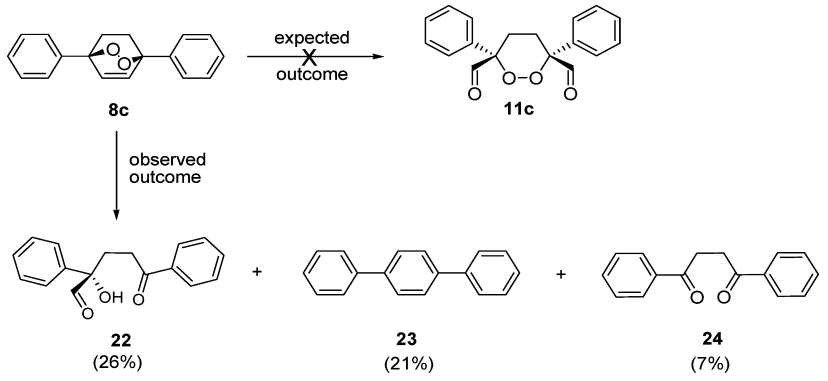
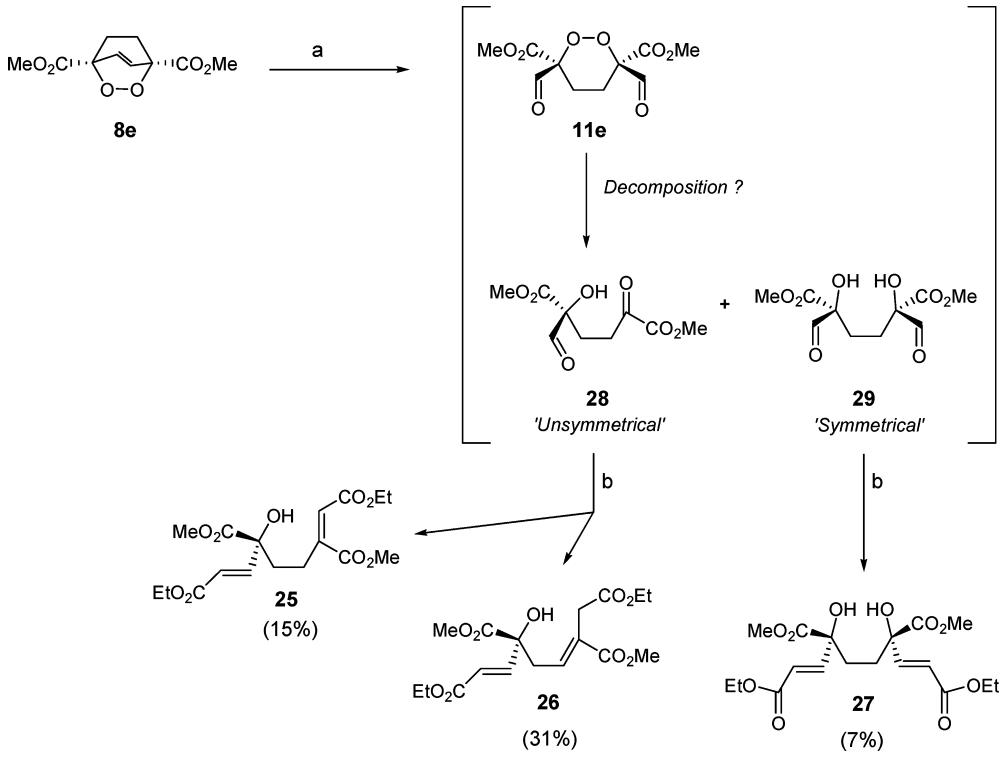
Scheme 8



Scheme 9



[a]1. O_3, DCM, −78 °C, 2. PPh_3 (1.1 equiv). [b]$Ph_3P{=}CHCO_2Et$ (2 equiv), DCM.

direct decomposition of the ozonide (and therefore not actually forming the dialdehydes at all) or via another sequence, and also to address the possibility that the rearrangements may be occurring due to the nature of the bridgehead substitution was to investigate these ozonolysis reactions under a different set of conditions, commonly known as "unsymmetrical ozonolysis". Consequently we decided to subject one dioxine that underwent rearrangement upon standard ozonolysis, **8e**, and one dioxine that gave the expected results, **8a**, to these alternative conditions.

Unsymmetrical ozonolysis was first reported by Schreiber et al. in 1982,[43] and as its name suggests results in two different functional groups being produced from the oxidative cleavage of an alkene, in this case, an aldehyde and an ester. The primary ozonide (molozonide) undergoes cleavage to produce the carbonyl/carbonyl oxide intermediate **30**. The alcohol then traps the carbonyl oxide to produce a hydroperoxy acetal, which is subsequently dehydrated to form an ester.[43,44] A key aspect of this reaction worth noting is that no ozonide is formed in contrast to "standard" ozonolysis.

To the best of our knowledge, the unsymmetrical ozonolysis protocol has not been previously reported on a 1,2-dioxine (either monocyclic or bicylic), however one would expect the product to be a dioxine incorporating aldehyde-ester functionalities, **32** (Scheme 10). If the two substituents (R and R^1) are different, then two regioisomers will be possible.

Treatment of **8a** to the unsymmetrical ozonolysis conditions, **8a** yielded the "expected" ester-aldehydes **33a** and **33b** in poor yield, with little selectivity seen between the two regioisomers, Scheme 11. The two isomers were easily separable via flash chromatography, and HMBC correlations were used to aid in the identification of the two isomers. In addition, **33a** was crystalline allowing for single crystal X-ray analysis, unambiguously confirming its structure and stereochemistry. Diketone **19**, which was seen as a byproduct in the standard ozonolysis of **8a** was also observed under these unsymmetrical conditions, in

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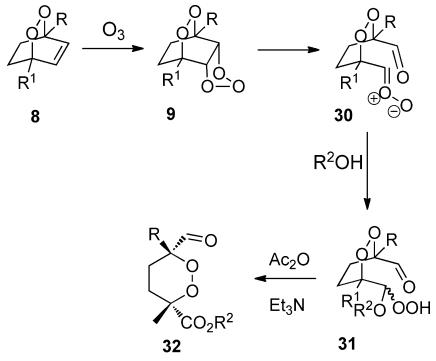
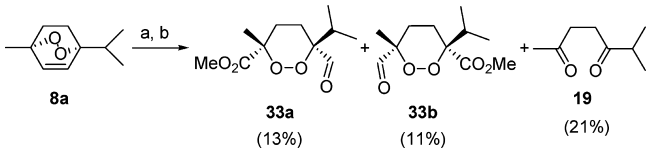
Scheme 10



Scheme 11



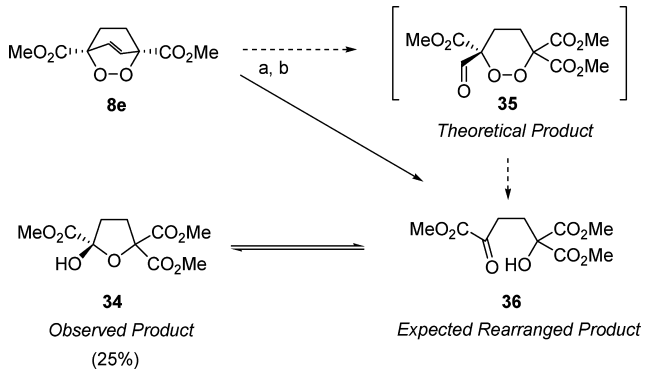
[a]O_3, DCM/MeOH (5:1), −78 °C. [b]NEt_3, Ac_2O.

21% yield. 1,2-Dioxane **33b** was an oil which showed early signs of decomposition thereby making purification difficult. The reason for this may be due to the *iso*-propyl flanking the aldehyde in **33a**, thereby creating a shielding effect aiding in protection against decomposition, whereas **33b**'s aldehyde moiety is adjacent to the smaller methyl group.

Only one major product, furan **34** was isolated upon subjecting **8e** to the unsymmetrical ozonolysis conditions. ^1H and ^{13}C NMR data showed that three ester groupings were present, but it was immediately evident through the lack of an aldehyde peak in the NMR spectra that the theoretically expected triester aldehyde **35** had not formed. It is likely that **34** exists in equilibrium with ketol **36**, resulting from a ring-opening rearrangement similar to that seen for the standard ozonolysis of **8e**, Scheme 12.

Formation of Diketone Products 19 and 24. The formation of two different diketone products were observed within this body of work. **19** was seen in both the standard and unsymmetrical ozonolysis of **8a**, being formed in 15 and 21% yield, respectively, while **24** was formed in 7% yield during the

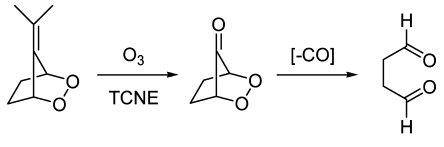
Scheme 12



[a]O_3, DCM/MeOH (5:1), −78 °C. [b]NEt_3, Ac_2O.

standard ozonolysis of **8c**. The respective 1,4-dicarbonyls were not observed in the ozonolysis of the other 1,2-dioxines (**8c**, **d** and **e**, **4** or **13**) employed within this study. 1,4-Dicarbonyls of this nature have previously been observed as byproduct of 1,2-dioxine chemistry. A recent example reported by our group found **19** and **24** were formed as the result of thermal decomposition of peroxide-diols involving a radical-induced homolytic cleavage of the peroxide followed by subsequent double β-scission.[14] It is unlikely that the formation of **19** and **24** in this instance resulted from this mechanistic process, due to the absence of either heat or light, thereby limiting the likelihood of a radical process. The ozonolysis of endoperoxide **37** in the presence of tetracyanoethylene was previously reported to furnish ketone **38**, which was unstable and readily decarbonylated at −10 °C to give succinaldehyde (**39**), Scheme 13.[45] Interestingly, formation of products **19** and **24**, **22**, **28** and

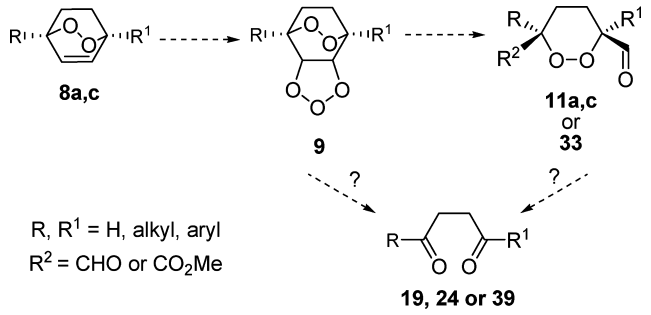
Scheme 13



36 within this study also require the loss of CO or CO_2 at some stage.

Reaction conditions common to both the symmetrical and unsymmetrical ozonolyses in our work was the use of weak base, namely triphenylphosphine or triethylamine. Although it is difficult to postulate how byproducts **19** and **24** were formed in this instance, there are several potential mechanistic pathways possible, including breakdown of either dioxine-aldehyde **11a**, **11c** or **33**, or alternatively and probably more likely, via decomposition of the molozonide intermediates **9**, Scheme 14. Their formation is beyond the scope of this study,

Scheme 14



however, is of mechanistic interest and will be the subject of more detailed investigations in the future.

Overall Mechanistic Scope and Insights for the Ozonolysis of Bicyclic 1,2-Dioxines. Overall we have seen steroid **4** reacted as "expected" toward ozone to furnish dialdehyde **7** in excellent (92%) yield, along with the dimethyl 1,2-dioxine **13** yielding the expected dicarbonyl **17** indicating that substituents on the double bond appear to be tolerated during these ozonolysis reactions. Of the bridgehead 1,2-dioxines investigated within this study, **8a**, **8b** and **8d** all reacteing as "expected" toward ozone to afford their respective dialdehydes (**11a**, **11b** and **11d**) in poor to good yields,

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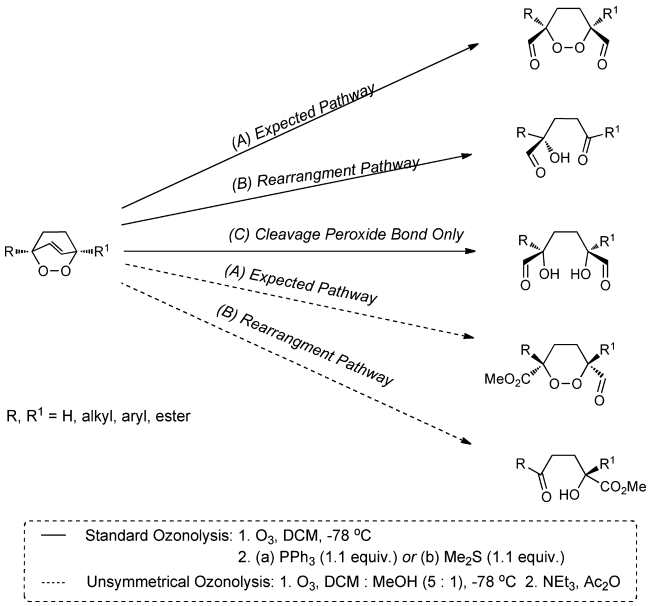
whereas ozonolysis of **8c** and **8e** resulted in a range of fragmentation products (**22** and **25**, **26**, **27**, respectively) showing a loss of either CO or CO_2 (depending on the proposed mechanism). Finally, unsymmetrical ozonolysis was utilized to further probe the reaction mechanism, with **8a** furnishing the expected aldehyde esters (**33a**,**b**), while **8e** once again resulted in formation of fragmentation product, **34**. A general summary of all outcomes is depicted in Scheme 15.

Scheme 15



It is apparent that the nature of the substituents plays a part in influencing the reaction outcome, as the alkyl substituted 1,2-dioxine **8a** did not rearrange under either standard or unsymmetrical ozonolysis, whereas the diester dioxine **8e** rearranged in both cases. It seems reasonable from our initial studies to postulate that electronic factors play an important part, with electron donating groups appearing to produce the expected dialdehydes, whereas upon removing electron density from the peroxide via electron withdrawing groups, rearrangements become dominant. It also appears plausible at this stage to propose that one bridgehead phenyl grouping (dioxine **8b**) has little effect on altering the reaction outcome, with normal ozonolysis proceeding, whereas two bridgehead phenyl moieties (dioxine **8c**) remove enough electron density to weaken the peroxide bonds and enable rearrangements to readily occur. Previous research has shown that reactions of alkenes with ozone are sensitive to electronic effects, with electron deficient alkenes having much lower rate constants than those alkenes with greater electron density.[46−48] This is believed to be due to the electrophilic nature of ozone, which adds to nucleophilic π-bonds of alkenes that are enriched by lone pair donation by electron donating groups, thereby assisting in the lowering of the activation barrier, and thus enhancing the reaction rate.[46,48] When the rate is increased, there is less chance for rearrangements to occur, making it reasonable to suggest that electron withdrawing groups attached to the bridgehead positions of these bicyclic 1,2-dioxines may assist in slowing the rate of reaction and thereby raising the likelihood of rearrangements.

Several of the reactions afforded products that showed the loss of CO or CO_2 (depending on the proposed mechanism), along with cleavage of the peroxide bond, with a similar mechanism appearing to be at play under both symmetrical and unsymmetrical ozonolysis conditions. In attempting to explain how these rearrangements occur, several questions are paramount. Do these rearrangements proceed via ozonide **10** decomposing into the expected dialdehydes **11** followed by facile rearrangement into **22**, **28** or **36**, Scheme 16, Pathway A, or, alternatively does ozonide **10** directly decompose into **22**, **28** or **36**, Scheme 16, Pathway B? Moreover, does the addition of PPh_3 assist in these rearrangements?

Since the resultant ozonide from the phenyl, phenyl disubstituted 1,2-dioxine **8c** rearranged upon treatment with both PPh_3 and Me_2S, it is unlikely that the bulky PPh_3 was solely responsible for the rearrangement seen under the standard ozonolysis conditions. As the unsymmetrical ozonolysis mechanism does not involve the formation of an ozonide, and since the same rearrangement was observed under unsymmetrical conditions, it is likely that the rearranged products do not arise directly from ozonide **10** under standard conditions, thereby ruling out Pathway B in Scheme 16. Pathway A is further supported by the two aldehyde peaks, with 1:1 integrations, that were seen in the crude ^{1}H NMR spectra from the ozonolysis of diester dioxine **8e**.

If dialdehyde **11**, or aldehyde esters **32**, **33** and **35** for unsymmetrical ozonolysis, are indeed forming (cannot be ruled out due to the low product yields) and spontaneously decomposing to furnish the rearranged products, there are several possibilities via how this could occur. Scheme 16 outlines a couple of potential pathways involving both concerted and stepwise mechanisms for Pathway A, both involving decarbonylation (−CO) of the aldehyde moiety. Decarbonylation of aldehydes is usually seen in the presence of transition metal catalysts,[49−51] or radical initiators.[52,53] There is no precedent for the loss of a carbonyl group α to a peroxide bond, making this type of rearrangement unique. At this stage, either a concerted or stepwise pathway is plausible.

Another mechanistic possibility is that either the aldehyde-carbonyl-oxide species **30** or the molozonide **9** may directly rearrange into products **22**, **28** or **36**, and may be induced by the electron withdrawing nature of the substituents (*vide supra*) Scheme 16 Pathways C and D respectively. These intermediates are common to both the symmetrical and unsymmetrical ozonolysis reactions, and involve a total loss of CO_2. It appears reasonable that decarboxylation via loss of the carbonyl oxide group from **30** is plausible, Scheme 16. Breakdown of the molozonide **9** into **22**, **28** or **36** could also occur via a concerted mechanism (Scheme 16, Pathway D), or through a series of stepwise reactions involving homolysis of the molozonide, 1,5-hydrogen atom abstraction with ring-opening, followed by loss of CO_2 to furnish compounds of type **22** or **36**.[54] While the formation of fragmentation products of type **22** was not the primary objective of this study, it is clear that there are several underlying rearrangements that may occur when 1,2-dioxines are treated with ozone, with Scheme 16 highlighting the most likely.

■ CONCLUSIONS

The ozonolysis of bicyclic 1,2-dioxines is an unusual and unique reaction and this study has clearly exemplified that the overall process of oxidative cleavage of the olefinic unit within 1,2-dioxines by ozone to furnish 1,4-dicarbonyl cyclic peroxides of

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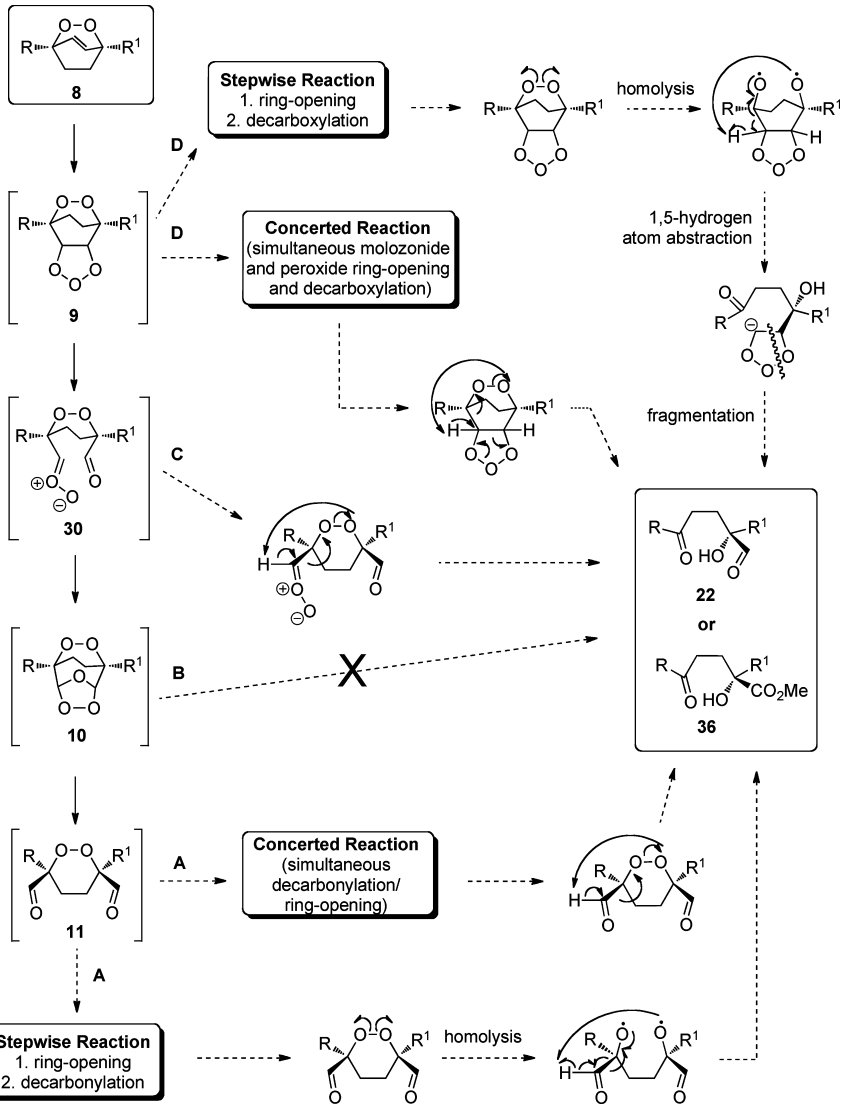
Scheme 16



type **11** is of general synthetic utility. Five of the seven bicyclic 1,2-dioxines furnished the desired 1,4-dialdehydes in moderate to excellent yields with a range of substitution and electronic patterns being explored. This study also elucidated for the first time several new background fragmentations and/or rearrangements that can occur upon treatment of 1,2-dioxines with ozone. While a full study into the genesis of these outcomes was not the primary purpose of this study, initial mechanistic studies have highlighted several plausible breakdown pathways as detailed within Scheme 16. Finally, we have also reported for the first time on the outcomes of several unsymmetrical ozonolyses of bicyclic 1,2-dioxines, which behaved in a similar manner to those of standard ozonolysis and as such further increases the synthetic scope and utility of these unique reactions.

EXPERIMENTAL SECTION

General Experimental Methods. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on either a 300 or 600 MHz instrument. TMS (0.00 ppm) and $CDCl_3$ (77.00 ppm) were used as internal standards. Melting Points are uncorrected. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh ASTM). Thin-layer chromatography (TLC) was performed using aluminum sheets of silica gel 60 F_{254} from Merck, and visualized under 254 nm light or developed in either vanillin or potassium permanganate dip. THF was distilled over sodium wire with benzophenone as indicator and freshly distilled prior to use. Ozone was generated from oxygen via corona discharge and all solutions purged with argon. Flow rates and ozone concentration levels were not recorded, as reactions proceeded until solutions were saturated with ozone. Compounds **4**,[55] **8a**,[56] **8b**,[14] **8c**,[57] **8d**[14] **19**,[58] **23**[59] and **24**[60] showed physical and chemical properties identical to those previously reported in the literature.

General Procedure for the Preparation of 1,2-Dioxines (4, 8a−e and 13). To a solution of the requisite 1,3-cyclohexadiene (**14**, **12a-e** or **15**) in dichloromethane (30 mL/g of 1,3-diene), in a custom-made pyrex flask fitted with a cooling jacket, was added rose bengal, *bis*(triethylammonium) salt (100 mg). Ice water was pumped throughout the cooling jacket to maintain a temperature of *ca* 5−10 °C within the reaction mixture at all times. Oxygen was bubbled through the solution, and the contents irradiated with 3 × 500 W tungsten halogen lamps until complete via TLC (1−8 h). The mixture was then concentrated *in vacuo* and the residue purified by flash chromatography. Any unreacted diene was also recovered at this time.

(±)-Dimethyl (1*R*,4*S*)-2,3-dioxabicyclo[2.2.2]oct-5-ene-1,4-dicarboxylate (8e). Colorless needles. Yield: 46%. Mp 66−68 °C. R_f 0.37 (3:7 ethyl acetate/hexane) ^{1}H NMR (300 MHz, $CDCl_3$): 6.88 (s, 2H), 3.86 (s, 6H), 2.56−2.49 (m, 2H), 1.83−1.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 168.6, 132.5, 77.9, 53.1, 26.3; IR (nujol)

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2927, 1745, 1306, 1119, 989, 702 cm^{-1}; HRMS calcd for $(M)^+$ $C_{10}H_{12}O_6$: 228.0634; found 228.0630.

(±)-(1*R*,4*S*)-1,5-Dimethyl-2,3-dioxabicyclo[2.2.2]oct-5-ene (13). Colorless oil. Yield 76%. R_f 0.27 (1:9 ethyl acetate/hexane). ^1H NMR (300 MHz, $CDCl_3$): 6.03 (s, 1H), 4.42 (m, 1H), 2.29 (m, 1H), 2.02 (m, 1H), 1.95 (s, 3H), 1.56−1.40 (m, 2H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 141.5, 128.9, 75.4, 75.2, 29.1, 23.1, 21.8, 18.5; IR (neat) 2932, 2360, 1660, 1444, 1374, 1224, 1158, 886, 764 cm^{-1}; LRP (+LSIMS) *m*/*z* (%) 190 (4), 173 (2), 158 (36), 155 (13), 141 (95), 125 (M^+, 13), 123 (100), 113 (9); HRMS calcd. for $(M + H)^+$ $C_8H_{13}O_2$: 141.0916; found 141.0910.

General Procedure for Ozonolysis of 1,2-Dioxines. A solution of 1,2-dioxine (**4**, **8a**−**e** or **13**) (3 mmol) in dichloromethane (50 mL) was cooled to −78 °C under a continuous atmosphere of argon. A stream of ozone was bubbled through the mixture until the solution turned pale blue. The mixture was bought back to ambient temperature, followed by the addition of triphenylphosphine (3.3 mmol). The resulting mixture was stirred at room temperature overnight and then concentrated *in vacuo* and the products were purified by flash chromatography.

(1*R*,3a*R*,3b*S*,5a*R*,7*S*,9a*R*,9b*R*,11a*R*)-3b,5a-diformyl-9a,11a-Dimethyl-1-(6-methylheptan-2-yl)tetradecahydro-1*H*-benzo[*c*]indeno[5,4-*e*][1,2]dioxin-7-yl Acetate (7). Colorless oil. Yield 92%. R_f 0.60 (3:7 ethyl acetate/hexane). ^1H NMR (300 MHz, $CDCl_3$): 10.01 (s, 1H), 9.62 (s, 1H), 5.28 (m, 1H), 2.83 (dd, 2H, *J* = 15.6, 3.6 Hz), 2.13 (m, 1H), 2.02 (s, 3H), 1.92−1.11 (m, 22H), 1.02 (s, 3H), 0.89 (d, 3H, *J* = 6.3 Hz), 0.87 (d, 3H, *J* = 1.2 Hz), 0.85 (d, 3H, *J* = 1.2 Hz), 0.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 202.5, 196.8, 169.8, 88.5, 87.7, 69.2, 56.5, 55.8, 45.8, 45.5, 40.5, 39.4, 35.7, 35.4, 35.2, 31.0, 28.8, 28.01, 27.96, 24.0, 23.6, 22.7, 22.5, 21.2, 19.8, 19.3, 18.3, 18.1, 13.2. Dialdehyde **7** decomposed readily over time thus was further characterized as triol **16**.

(1*R*,3a*R*,3b*S*,5a*R*,7*S*,9a*R*,9b*R*,11a*R*)-3b,5a-Bis-(hydroxymethyl)-9a,11a-dimethyl-1-(6-methylheptan-2-yl)-tetradecahydro-1*H*-benzo[*c*]indeno[5,4-*e*][1,2]dioxin-7-ol (16). To a solution of dialdehyde (**7**) (648 mg, 1.32 mmol) in anhydrous THF (5 mL) at 0 °C under an atmosphere of nitrogen was added $LiAlH_4$ (215 mg, 5.67 mmol) in portions, with stirring. The mixture was kept at 0 °C until TLC showed the disappearance of the starting material (60 min). The mixture was quenched with saturated NH_4Cl (5 mL) and diluted with diethyl ether (10 mL). The mixture was then acidified to pH 1 with the addition of HCl (2 M, few drops). The layers were separated and the aqueous layer extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography to furnish a white solid (106 mg, 55%) (**16**). Mp 174−175 °C. R_f 0.27 (6:4 ethyl acetate/hexane). $[\alpha]_D^{20}$ = +111.76 (*c* 0.34, THF). ^1H NMR (300 MHz, $CDCl_3$): 4.61 (d, 1H, *J* = 12.3 Hz), 4.33 (s, 1H), 3.90 (d, 2H, *J* = 12.9 Hz), 3.48 (d, 1H, *J* = 12.3 Hz), 2.67 (dd, 1H, *J* = 15, 3 Hz), 2.41−1.06 (m, 27H), 1.01 (s, 3H), 0.93 (d, 3H, *J* = 10.8 Hz), 0.90 (s, 3H), 0.87 (d, 3H, *J* = 1.2 Hz), 0.85 (d, 3H, *J* = 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 85.8, 85.2, 67.3, 64.6, 61.7, 57.8, 56.8, 45.5, 45.3, 41.6, 39.4, 35.8, 35.38, 35.35, 31.2, 29.0, 28.2, 28.0, 27.5, 23.7, 22.8, 22.5, 21.2, 18.9, 18.8, 18.4, 13.9; IR (nujol) 3313, 2927, 1464, 1379, 1059, 1034 cm^{-1}; HRMS calcd. for $(M + NH_4)^+$ $C_{27}H_{51}NO_5$: 470.3840; found 470.3835.

(±)-(3*R*,6*S*)-6-Acetyl-3-methyl-1,2-dioxane-3-carbaldehyde (17). Pale-yellow oil. Yield 45%. R_f 0.46 (3:7 ethyl acetate/hexane). ^1H NMR (300 MHz, $CDCl_3$): 9.75 (d, 1H, *J* = 1.8 Hz), 4.55 (dd, 1H, *J* = 11.7, 3.0 Hz), 2.39 (m, 1H), 2.14 (s, 3H), 1.95 (m, 1H), 1.75−1.51 (m, 2H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 204.0 202.2, 85.8, 85.3, 27.9, 26.4, 22.8, 19.8; IR (neat) 2934, 2360, 1724, 1446, 1363, 1115, 935, 749 cm^{-1}; LRP (+LSIMS) *m*/*z* (%) 295 (20), 279 (33), 255 (9), 215 (12), 211 (97), 195 (100), 181 (22), 173 (M^+, 2), 139 (36), 123 (19) HRMS calcd. for $(M + H)^+$ $C_8H_{13}O_4$: 173.0814; found 173.0808.

(±)-(3*R*,6*R*)-3-Methyl-6-(propan-2-yl)-1,2-dioxane-3,6-dicarbaldehyde (11a). Colorless oil. Decomposes readily. Typically the crude sample was used immediately for Wittig protection and subsequent full characterization. R_f 0.52 (3:7 ethyl acetate/hexane). A small amount was able to be isolated for NMR analysis before decomposition. ^1H NMR (300 MHz, $CDCl_3$): 9.69 (s, 1H), 9.42 (s, 1H), 2.12−2.03 (m, 2H), 1.85−1.78 (m, 2H), 1.59 (m, 1H), 1.44 (s, 3H), 0.98 (d, 3H, *J* = 7.2 Hz), 0.97 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 202.7, 199.1, 89.1, 84.4, 31.8, 24.4, 19.5, 17.3, 16.3, 15.9.

(±)-(3*R*,6*R*)-3-Phenyl-1,2-dioxane-3,6-dicarbaldehyde (11b). Colorless oil. Decomposes readily. Typically the crude sample was used immediately for Wittig protection and subsequent full characterization. Yield 33%. R_f 0.38 (1:1 ethyl acetate/hexane). A small amount was able to be isolated for NMR analysis before decomposition. ^1H NMR (300 MHz, $CDCl_3$): 9.69 (d, 1H, *J* = 1.5 Hz), 9.61 (s, 1H), 7.52−7.30 (m, 5H), 4.69 (dd, 1H, *J* = 11.1, 3.0 Hz), 2.84 (m, 1H), 2.18−1.79 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 197.7, 197.0, 129.2, 129.1, 129.0, 128.6, 125.4, 125.2, 89.0, 84.7, 26.6, 21.3.

(±)-Dimethyl-2,2′-[(3*R*,6*S*)-3,6-diformyl-1,2-dioxane-3,6-diyl]diacetate (11d). Purification and characterization proved difficult, as the sample decomposed upon attempted column chromatography. Typically the crude sample was used immediately for Wittig protection and subsequent full characterization. R_f 0.61 (7:3 ethyl acetate/hexane).

General Procedure for Wittig Reaction of Ozonolysis Products. To a solution of dialdehyde (**11a,b,** or **d**) (3 mmol) in dichloromethane (50 mL) under an atmosphere of nitrogen was added ethyl 2-(triphenylphosphanylidene) acetate (6 mmol). The mixture was stirred at ambient temperature until complete by ^1H NMR or TLC. The mixture was then concentrated *in vacuo* and the products purified by flash chromatography.

(±)-Ethyl-(2*E*)-3-[(3*R*,6*R*)-6-formyl-3-methyl-6-(propan-2-yl)-1,2-dioxan-3-yl]prop-2-enoate (18a). Colorless oil. Yield 44% (over three steps: ozonolysis, reduction and Wittig). R_f 0.55 (1:4 ethyl acetate/hexane). ^1H NMR (600 MHz, $CDCl_3$): 9.74 (br s, 1H), 6.72 (d, 1H, *J* = 16.2 Hz), 5.84 (d, 1H, *J* = 16.2 Hz), 4.19 (q, 2H, *J* = 7.2 Hz), 2.09 (ddd, 1H, *J* = 13.8, 5.4, 2.4 Hz), 1.93 (sept 1H, *J* = 7.2 Hz), 1.81 (m, 1H), 1.69 (apt dt, 1H, *J* = 13.2, 4.8 Hz), 1.63 (ddd, 1H, *J* = 13.8, 5.4, 3.0 Hz), 1.52 (s, 3H), 1.28 (t, 3H, *J* = 7.2 Hz), 0.97 (d, 3H, *J* = 7.2 Hz), 0.93 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): 204.0, 166.1, 148.4, 120.3, 89.1, 79.0, 60.6, 32.3, 29.4, 20.8, 19.8, 16.3, 15.7, 14.1; IR (neat) 2976, 1723, 1655, 1369, 1309, 1184, 1036, 749 cm^{-1}; LRP (+LSIMS) *m*/*z* (%) 271 (M^+, 8), 258 (10), 242 (12), 225 (100), 195 (12), 179 (50); HRMS calcd. for $(M + H)^+$ $C_{14}H_{23}O_5$: 271.1545; found 271.1535.

(±)-Ethyl-(2*E*)-3-[(3*R*,6*R*)-6-formyl-6-phenyl-1,2-dioxan-3-yl]-prop-2-enoate (18b). Colorless oil. Yield 10% (over three steps: ozonolysis, reduction and Wittig). R_f 0.61 (dichloromethane). ^1H NMR (300 MHz, $CDCl_3$): 9.71 (d, 1H, *J* = 2.1 Hz), 7.43−7.30 (m, 5H), 6.74 (dd, 1H, *J* = 16.2, 5.1 Hz,), 5.98 (dd, 1H, *J* = 16.2, 1.6 Hz,), 4.88 (m, 1H), 4.21 (q, 2H, *J* = 7.2), 2.87 (m, 1H), 2.06−1.74 (m, 3H), 1.30 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 198.8, 165.7, 142.0, 134.9, 129.0, 125.1, 123.2, 88.6, 79.7, 60.8, 27.8, 26.5, 14.2 (3 aromatic C masked); IR (neat) 2987, 1724, 1658, 1452, 1309, 1275, 1193, 1036, 700 cm^{-1}; FTMS (+ESI) *m*/*z* (%): 291 (M^+, 4) 279 (5), 277 (12), 262 (16), 261 (100), 259 (2); HRMS calcd. for $(M + H)^+$ $C_{16}H_{19}O_5$: 291.1232; found 291.1229.

(±)-Diethyl-(2*E*,2′*E*)-3,3′-[(3*R*,6*S*)-3,6-*bis*(2-methoxy-2-oxoethyl)-1,2-dioxane-3,6-diyl]bisprop-2-enoate (18d). Colorless oil. Yield 21% (over three steps: ozonolysis, reduction and Wittig). R_f 0.51 (1:1 ethyl acetate/hexane). ^1H NMR (50 °C, 300 MHz, $CDCl_3$): 6.93 (d, 2H, *J* = 16.2 Hz), 6.00 (d, 2H, *J* = 16.2 Hz), 4.20 (q, 4H, *J* = 7.2 Hz), 3.67 (s, 6H), 2.92−2.63 (m, 4H), 2.23−2.15 (m, 2H), 1.95−1.88 (m, 2H), 1.29 (t, 6H, *J* = 7.2 Hz); ^{13}C NMR (50 °C, 75 MHz, $CDCl_3$): 169.1, 165.8, 146.4, 122.2, 80.3, 60.6, 51.7, 41.1, 27.1, 14.1; IR (neat) 2955, 1720, 1656, 1438, 1311, 1179, 1034, 865, 731 cm^{-1}; LRP (+LSIMS) *m*/*z* (%): 857 (10), 429 (M^+, 100), 412 (19), 337 (8), 235 (50); HRMS calcd. for $(M^+ + H)^+$ $C_{20}H_{29}O_{10}$: 429.1761; found 429.1752.

(±)-[(3*R*,6*R*)-3-Methyl-6-(propan-2-yl)-1,2-dioxane-3,6-diyl]-dimethanediyl Diacetate (21). Ozonolysis was performed on ascaridole (**8a**) (260 mg, 1.55 mmol) and reduced with triphenylphosphine (407 mg, 1.55 mmol) via the general method to afford a

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crude oily solid. This was triturated with hexane to give a crude yellow oil (141 mg). To a stirred solution of this crude dialdehyde (141 mg, 0.70 mmol (assuming 100% product)) in anhydrous THF (5 mL) at 0 °C under an atmosphere of nitrogen was added $LiAlH_4$ (80 mg, 2.11 mmol) in portions, with stirring. The resulting mixture was stirred at 0 °C until TLC showed the disappearance of the starting material (30 min). The solution was quenched with saturated NH_4Cl (5 mL) and diluted with diethyl ether (10 mL). The mixture was acidified to pH 1 with the addition of conc. HCl (2 M, 2 drops). The layers were separated and the aqueous layer extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. To this crude mixture of diol **20** was added pyridine (1 mL), acetic anhydride (0.64 g, 6.34 mmol) and DMAP (17 mg, 0.14 mmol), and the resulting mixture stirred overnight. The mixture was diluted with dichloromethane (5 mL) and washed with 10% HCl (5 mL). The organic layer was then removed and the aqueous layer extracted with dichloromethane (3 × 5 mL). The organic layers were combined, washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified via flash chromatography to afford a colorless oil (65 mg, 32%) (**21**). R_f 0.57 (3:7 ethyl acetate/hexane). ^{1}H NMR (50 °C, 300 MHz, $CDCl_3$): 4.28 (d, 1H, J = 12.3 Hz), 4.16 (d, 1H, J = 12.3 Hz), 4.10 (br s, 2H), 2.23 (m, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 1.82−1.54 (m, 4H), 1.27 (s, 3H), 0.97 (d, 6H, J = 6.9 Hz); ^{13}C NMR (50 °C, 75 MHz, $CDCl_3$): 170.6 (×2 overlapping), 82.4, 78.8, 67.3, 63.1, 31.9, 26.5, 22.0, 20.8, 20.7, 19.9, 16.7, 16.6; IR (neat): 2974, 2364, 1747, 1458, 1377, 1246, 1049 cm^{-1}; LRP (+LSIMS) m/z (%): 530 (67), 475 (9), 338 (26), 289 (M^+, 35), 243 (24) (219 (100). HRMS calcd. for $(M + H)^+$ $C_{14}H_{25}O_6$: 289.1651; found 289.1639.

(±)-(2*S*)-2-Hydroxy-5-oxo-2,5-diphenylpentanal (22).

Method A: Reduction with PPh_3. Followed general procedure outline for the ozonolysis of 1,2-dioxines.

Method B: Reduction with Me_2S. A solution of 1,2-dioxine (**8c**) (3 mmol) in dichloromethane (50 mL) was cooled to −78 °C under a continuous atmosphere of argon. A stream of ozone was bubbled through the mixture until the solution turned pale blue. The mixture was bought back to room temperature and placed under an atmosphere of nitrogen. Dimethyl disulfide (3.3 mmol) was slowly added, and the resulting mixture was stirred at room temperature overnight. The mixture was then concentrated *in vacuo* and the products purified by flash chromatography.

Colorless needles. Yield 26%. Mp 82−84 °C. R_f 0.29 (1:4 ethyl acetate/hexane) ^{1}H NMR (300 MHz, $CDCl_3$): 9.64 (d, 1H, J = 1.2 Hz), 7.93−7.89 (m, 2H), 7.58−7.30 (m, 8H), 4.34 (d, OH, J = 1.2 Hz), 3.14 (dt, 1H, J = 18.2, 7.5 Hz), 3.02 (dt, 1H, J = 18.2, 6.6 Hz), 2.52 (dd, 2H, J = 7.5, 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 200.1, 199.7, 138.0, 136.4, 133.4, 128.9, 128.6, 128.1, 128.1, 125.8, 81.0, 32.2, 30.7; IR (nujol) 3448, 2927, 2859, 1722, 1676, 741 cm^{-1}; LRP (+LSIMS) m/z (%) 269 (M^+, 1), 239 (100), 221 (24), 193 (9), 178 (7), 161 (43), 133 (18), 115 (23), 105 (87), 77 (48); HRMS calcd. for $(M)^+$ $C_{17}H_{16}O_3$: 268.1099; found 268.1105.

(±)-1,7-Diethyl-3-methyl (1*E*,3*S*)-3-hydroxy-6-propanoylhepta-1,6-diene-1,3,7-tricarboxylate (25). Colorless oil. Yield 15% (over three steps: ozonolysis, reduction and Wittig). R_f 0.69 (1:1 ethyl acetate/hexane) ^{1}H NMR (600 MHz, $CDCl_3$): 6.99 (d, 1H J = 15.3 Hz), 6.77 (s, 1H), 6.27 (d, 1H J = 15.3 Hz), 4.24 (q, 2H, J = 7.2 Hz), 4.19 (q, 2H, J = 7.2 Hz), 3.82 (s, 3H), 3.81 (s, 3H), 2.89−2.80 (m, 2H), 2.10 (ddd, 1H, J = 15.9, 9.9, 6.6 Hz), 1.96 (ddd, 1H, J = 15.9, 9.9, 6.6 Hz), 1.31 (t, 3H, J = 7.2 Hz), 1.29 (t, 3H, J = 7.2 Hz) (hydroxl proton not detected); ^{13}C NMR (150 MHz, $CDCl_3$): 174.0, 166.8, 166.1, 165.5, 146.7, 146.1, 127.7, 121.8, 76.8, 60.9, 60.5, 53.3, 52.5, 37.4, 22.3, 14.1, 14.0; IR (neat) 3497, 2956, 1711, 1647, 1438, 1263, 1176, 1028, 983, 732 cm^{-1}; LRP (+LSIMS) m/z (%) 373 (M^+, 100), 355 (19), 327 (30), 309 (34), 295 (32), 281 (74), 267 (36), 249 (28), 235 (25), 221 (60), 207 (68); HRMS calcd. for $(M + H)^+$ $C_{17}H_{25}O_9$: 373.1499; found 373.1499.

(±)-1,7-Diethyl-3-methyl (1*E*,3*S*,5*E*)-3-hydroxy-6-propanoylhepta-1,5-diene-1,3,7-tricarboxylate (26). Colorless oil. Yield 31% (over three steps: ozonolysis, reduction and Wittig). R_f 0.57 (1:1 ethyl acetate/hexane) ^{1}H NMR (600 MHz, $CDCl_3$): 6.94 (d, 1H, J = 15.6 Hz), 6.25 (d, 1H, J = 15.6 Hz), 5.83 (t, 1H, J = 1.5 Hz), 4.21 (q, 2H, J = 7.2 Hz), 4.18 (q, 2H, J = 7.2 Hz), 3.84 (s, 3H), 3.82 (s, 3H) 3.51 (s, 1OH), 2.46 (m, 1H), 2.31 (m, 1H), 2.05 (m, 1H), 1.97 (m, 1H), 1.30 (t, 3H, J = 7.2 Hz), 1.27 (t, 3H, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): 173.8, 168.7, 165.9, 164.7, 148.0, 146.1, 122.5, 120.9, 76.4, 60.8, 60.7, 53.8, 52.4, 35.9, 28.2, 14.2, 14.1; IR (neat) 3484, 2957, 1717, 1437, 1259, 1173, 1030, 983, 735 cm^{-1}; LRP (+LSIMS) m/z (%) 373 (M^+, 100), 341 (17), 327 (32), 309 (5), 295 (44), 281 (26), 263 (12), 249 (18), 235 (12), 221 (13), 207 (14); HRMS calcd. for $(M + H)^+$ $C_{17}H_{25}O_9$: 373.1499; found 373.1502.

(±)-1,6-Dimethyl-3,4-dideoxy-2,5-bis-*C*-[(1*E*)-3-ethoxy-3-oxoprop-1-en-1-yl]-D-*erythro*-hexarate (27). Colorless oil. Yield: 7% (over three steps: ozonolysis, reduction and Wittig). R_f 0.48 (1:1 ethyl acetate/hexane). ^{1}H NMR (600 MHz, $CDCl_3$): 6.93 (d, 2H, J = 15.3 Hz), 6.23 (d, 2H, J = 15.3 Hz), 4.21 (q, 4H, J = 7.2 Hz), 3.83 (s, 6H), 3.52 (s, 2H), 1.95 (dd, 2H, J = 13.8, 4.8 Hz), 1.72 (dd, 2H, J = 13.8, 4.8 Hz), 1.30 (t, 6H, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): 174.0, 166.0, 146.4, 122.3, 76.5, 60.7, 53.7, 32.4, 14.2; IR (neat) 3458, 2958, 1710, 1437, 1231, 1105, 996 cm^{-1}; LRP (+LSIMS) m/z (%) 403 (M+, 100), 369 (18), 327 (32), 311 (21), 281 (28), 251 (15), 235 (20), 219 (27), 191 (23); HRMS calcd. for $(M + H)^+$ $C_{18}H_{27}O_{10}$: 403.1604; found 403.1602.

Attempted Isomerization of 25 and 26.

Method A: Heat. An NMR tube containing **25** (10 mg) or **26** (27 mg) in $CDCl_3$ was heated to 60 °C, and the temperature was maintained for 7 h. No change was detected for either sample via TLC or ^{1}H NMR.

Method B: Heat and Acidic Conditions. An NMR tube containing **25** (10 mg) or **26** (27 mg) in $CDCl_3$ with a catalytic amount (10 mol %) of PTSA was heated to 60 °C, and the temperature was maintained for 6 h. No change was detected for either sample via TLC or ^{1}H NMR.

General Procedure for Unsymmetrical Ozonolysis of 1,2-Dioxines. An ozone stream was bubbled through a stirred suspension of 1,2-dioxine **8a** or **8e** (1 mmol) and $NaHCO_3$ (0.5 mmol) in a 5: 1 mixture of CH_2Cl_2:MeOH (10 mL) at −78 °C under an atmosphere of argon, until the solution turned pale blue. The solution was bought back to room temperature. The $NaHCO_3$ was filtered off and the mother liqueur concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (10 mL) and cooled to 0 °C. Triethylamine (1.5 mmol) and acetic anhydride (3 mmol) were then added, and the solution brought to room temperature and stirred for 1 h. This mixture was treated with methanol (1 mL), stirred for 15 min and then diluted with diethyl ether (5 mL) and washed with 5% H_2SO_4 (3 × 10 mL), saturated $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by flash chromatography.

(±)-Methyl-[(3*R*,6*R*)-6-formyl-3-methyl-6-(propan-2-yl)-1,2-dioxan-3-yl]acetate (33a). Colorless crystals. Yield 13%. R_f 0.70 (3:7 ethyl acetate/hexane). Mp 64−66 °C. ^{1}H NMR (600 MHz, $CDCl_3$): 9.71 (br d, 1H, J = 1.5 Hz), 3.71 (s, 3H), 2.10−1.74 (m, 5H), 1.58 (s, 3H), 0.94 (d, 3H, J = 6.9 Hz), 0.92 (d, 3H, J = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): 203.5, 171.7, 89.2, 81.2, 52.5, 32.1, 27.3, 19.9, 19.8, 16.3, 15.8; IR (neat) 2971, 1738, 1456, 1374, 1288, 1248, 1123, 748 cm^{-1}; LRP (+LSIMS) m/z (%): 483 (22), 304 (30), 269 (16), 248 (100), 231 (5), 186 (23); HRMS calcd. for $(M + H)^+$ $C_{11}H_{19}O_5$: 231.1232; found 231.1227.

(±)-Methyl-[(3*S*,6*R*)-6-formyl-6-methyl-3-(propan-2-yl)-1,2-dioxan-3-yl]acetate (33b). Colorless oil. Yield 11%. R_f 0.53 (3:7 ethyl acetate/hexane). ^{1}H NMR (600 MHz, $CDCl_3$): 9.58 (s, 1H), 3.78 (s, 3H), 2.41−2.32 (m, 1H), 2.14−1.98 (m, 4H), 1.32 (s, 3H), 0.99 (d, 3H, J = 7.2) 0.97 (d, 3H, J = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): 200.9, 170.8, 87.4, 84.6, 52.1, 31.9, 24.9, 22.7, 18.2, 16.9, 16.8; IR (neat) 2972, 1737, 1444, 1372, 1243, 1043, 754 cm^{-1}; LRP (+LSIMS) m/z (%): 231 (M^+, 10), 201 (5), 185 (21), 171 (8), 155 (100), 143 (19); HRMS calcd. for $(M + H)^+$ $C_{11}H_{19}O_5$: 231.1232; found 231.1240.

(±)-Trimethyl-(5*S*)-5-hydroxydihydrofuran-2,2,5(3*H*)-tricarboxylate (34). Colorless waxy oil. Yield: 25%. R_f 0.52 (3:7 ethyl acetate/hexane). ^{1}H NMR (600 MHz, $CDCl_3$): 4.26 (s, OH), 3.84 (s,

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3H), 3.82 (s, 3H), 3.80 (s, 3H), 2.74−2.68 (m, 2H), 2.54 (dt, 1H, J = 13.2, 9 Hz), 2.17 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): 169.4, 169.2, 168.4, 104.1, 87.3, 53.4, 53.3, 53.2, 34.4, 32.2; IR (neat) 3471, 2964, 2364, 1749, 1441, 1288, 1209, 1076, 1016, 669 cm^{-1}; LRP (+LSIMS) m/z (%): 295 (18), 267 (30), 245 ((M − OH)$^-$, 33), 221 (100), 204 (33), 193 (33), 185 (34); HRMS calcd. for (M − OH)$^-$ $C_{10}H_{13}O_7$: 245.0661; found 245.0666.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic data for compounds **22** and **33a**; ^{1}H and ^{13}C NMR data for compounds **8e**, **13**, **7**, **16**, **17**, **11a**, **18a**, **18b**, **22**, **25**, **26**, **27**, **33a** and **34**; VT ^{1}H and ^{13}C NMR data for compounds **18d** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(54) During the examination of this work, a reviewer suggested that we may wish to consider an alternative heterolytic pathway for formation of compounds of type **22** from **8c** that involved the loss of CO_2 during the reaction sequence. While the examiner and we concur

that such an alternative cannot explain the formation of all of the unusual products of similar type to **22**, it is worthy of consideration. Thus, Richardson demonstrated that 2-alkylperoxyalkanols undergo a relatively facile base-catalyzed fragmentation with loss of a formaldehyde/aldehyde moiety (Richardson, W. H.; Heeson, T. C. *J. Org. Chem.* **1972**, *37*, 3416−3419.). In our study, the necessary alcohol for the Richardson-type fragmentation could be generated from either hydration or reversible nucleophilic addition to the aldehyde-substituted 1,2-dioxines. This mechanism can also occur equally well on the products of nonsymmetrical ozonolysis since one end will always contain a peroxy aldehyde.

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