MICROREVIEW

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End-Group-Differentiating Ozonolysis of Norbornene Systems To Afford Highly Substituted Cyclopentane Rings

Sebastián A. Testero,*[a] María I. Mangione,[a] Alejandra G. Suárez,[a] and Rolando A. Spanevello*[a]

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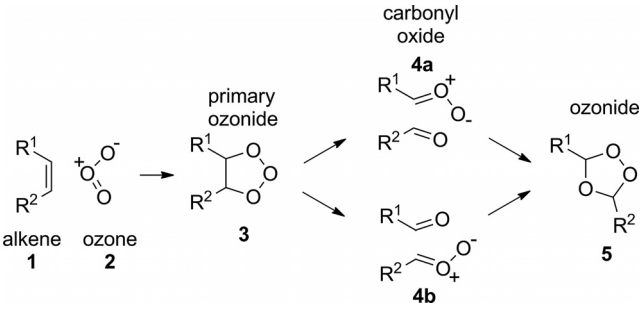
The end-group-differentiating ozonolysis concept is discussed, with an emphasis on norbornene systems. Different remote functional groups in *endo* positions in norbornene derivatives are able to direct the primary ozonide fragmentation. By analysis of the factors affecting the regioselectivity, a rule to predict the direction of the primary ozonide rupture is formulated. These reactions give access to highly substituted cyclopentane rings and provide opportunities for their subsequent regioselective manipulation.

Introduction

Ozonolytic end-group-differentiating cleavage of alkenes is an emerging area in which the scope of traditional ozonolysis as a classic organic reaction is being broadened.

The first reported ozonolysis of an unsaturated organic compound dates to the middle of the XIX century, when Schönbein reported the ozonolysis of ethylene to give carbonic acid, formaldehyde, and formic acid.[1] Despite the long time that it has been known, different aspects of this reaction class remain unexplored. The reactions involve the cleavage of multiple carbon–carbon or carbon–heteroatom bonds. Even though there are many alternatives, ozonolysis remains a clean, cost-effective, sustainable, and highly atom-efficient oxidative transformation.[2]

Extensive investigation of the mechanism of alkene ozonolysis has confirmed the basic pathway originally proposed by Criegee[3] in his seminal work done several decades ago. The most thoroughly developed proposal for the Criegee mechanism involves three steps (Scheme 1): i) [3+2] dipolar cycloaddition between ozone and the alkene, leading to formation of a primary ozonide (PO, the 1,2,3-trioxolane **3**), ii) a cycloreversion process to provide a transient carbonyl oxide and a stable carbonyl compound, which in cases of unsymmetrically substituted alkenes might proceed in two different ways (**4a** and **4b**), and iii) recombination of the carbonyl oxide and the carbonyl compound to give what is traditionally described as an ozonide (the 1,2,4-trioxolane **5**).

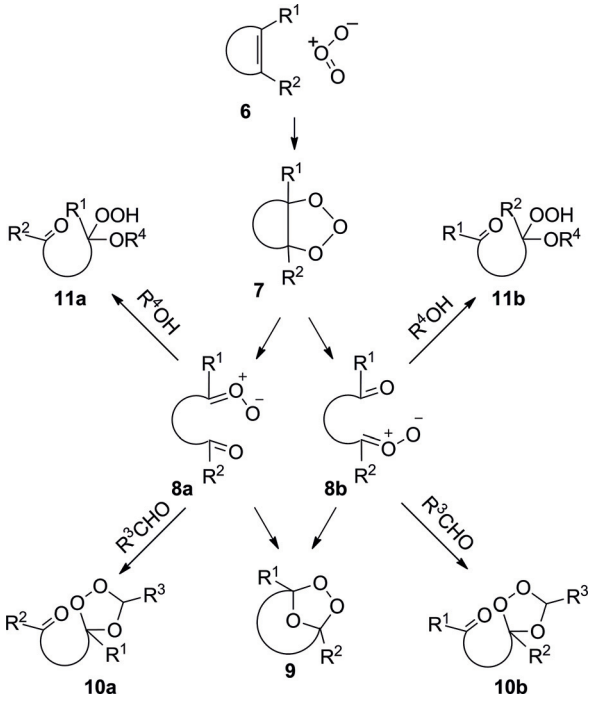


Scheme 1. Overview of alkene ozonolysis.

The carbonyl oxides **4a**, **b** that are assumed to be produced by spontaneous fragmentation of the primary ozonides, even at low temperatures, are considered the crucial species to the mechanism of ozonolysis. Even though the intermediates have never been directly detected in situ, sufficient evidence in support of their role in the Criegee mechanism has accumulated.[3] These transient intermediates species can display some diradical or zwitterionic character, depending upon reaction conditions.[4] Throughout this work, arbitrarily, the zwitterionic representation is used.

In a classical ozonolysis reaction the carbonyl oxide is trapped by the co-generated carbonyl group to give a 1,2,4-trioxolane of type **9** (Scheme 2). Alternatively, the transient carbonyl oxides **8a**, **8b** could also be trapped by other carbonyl derivatives present in the reaction medium, producing so-called cross ozonides **10a**, **10b** (see Scheme 2). When the ozonolysis is carried out in a participating solvent, such as methanol, the intermediate carbonyl oxides **8a** and **8b** are trapped by the alcohol to yield the α-alkoxy-hydroxyperoxides **11a** and **11b**.

[a] Instituto de Química Rosario (CONICET), Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario,
Suipacha 531, S2002LRK Rosario, Argentina
Fax: +54-341-4370477
E-mail: testero@iquir-conicet.gov.ar
spanevello@iquir-conicet.gov.ar
Homepage: http://www.iquir-conicet.gov.ar/eng/pers2.php?campo1=171&area=13



Scheme 2. Possible routes of alkene ozonolysis.

Once cleavage of the PO is attained and the carbonyl oxide trapped, the identity of the product depends on the further reaction conditions applied (Scheme 3). The hydroxyperoxides **12** can, for instance, be dehydrated with acetic anhydride and triethylamine to produce the aldehyde-esters **13** or, alternatively, addition of *p*-toluenesulfonic acid to the reaction medium leads to the formation of the acetal-alkoxy hydroperoxides **14**. Neutralization of the acidic reaction medium with $NaHCO_3$, followed by reduction of peroxyacetals **14** with dimethyl sulfide, yields acetal-aldehydes **15**. Dehydration of **14** under the same conditions as for **12** affords acetal-esters **16**.

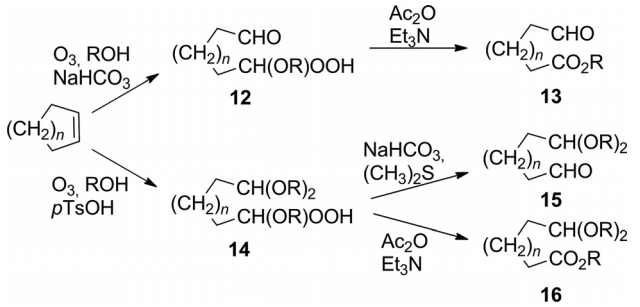
Ozonolytic end-group differentiation cleavage has been used as a key step in the challenging construction of highly substituted cyclopentane rings, which are found in many biologically active natural products such as prostaglandins, alkaloids, carbocyclic nucleosides, and carbasugars.[5] An appealing strategy by which to access these highly substituted cyclopentanes is a sequential combination of a stereoselective Diels–Alder cycloaddition to afford a conformationally rigid substituted bicyclic system of type **19**, followed by oxidative cleavage of the double bond of the norbornene (Scheme 4). If end-group-differentiating ozonolysis is applied to appropriately functionalized norbornene derivatives, cyclopentane rings bearing two different functional

Sebastián A. Testero completed his Ph.D. in synthetic organic chemistry at the Instituto de Química Rosario in 2005, under the supervision of Prof. R. A. Spanevello. He then carried out postdoctoral research in solid-phase synthesis with Prof. E. G. Mata at the same institute. Between 2007 and 2011 he was a postdoctoral research associate at the University of Notre Dame at the Mobashery lab working in medicinal chemistry. Since 2011 he has been an adjunct researcher of the Argentine National Council of Research. His research interests center on medicinal chemistry, combinatorial chemistry, ozonolysis, and organometallic chemistry including metathesis and gold catalysis.

María Inés Mangione completed her Ph.D. in synthetic organic chemistry at the Instituto de Química Rosario in 2006, under the supervision of Prof. R. A. Spanevello. Between 2006 and 2010 she worked as head of research at Synthon Argentina, a pharmaceutical company. Since mid-2010 she has been an assistant researcher of the Argentine National Council of Research. Her research interests center on nanotechnology, planning and designing of organic dendrimers for optoelectronic applications, ozonolysis, and glycosylation reactions.

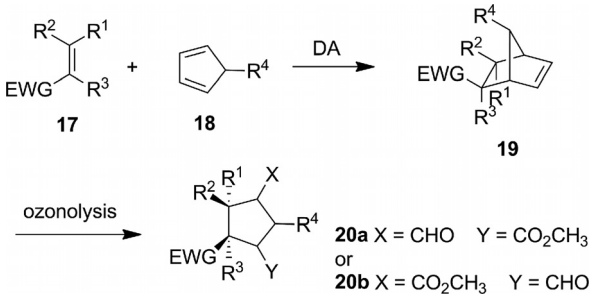
Alejandra G. Suárez obtained her Ph.D. degree in 1990 under the supervision of Prof. Angela Suárez at the Universidad Nacional de Córdoba, Argentina. She then undertook postdoctoral work at the École Normale Supériere in Paris under the guidance of Drs. Christian Amatore and Anny Jutand and later in the group of Prof. Malcolm L. H. Green at the University of Oxford, UK. She is Professor of Organic Chemistry at the Universidad Nacional de Rosario. Since 2009 she has been a member of the Scientific Advisory Board of the OPCW, The Hague. Her main research interest is focused on the sustainable production of materials from biomass for application in asymmetric synthesis.

Rolando A. Spanevello received his degree in industrial chemistry from Pontificia Universidad Católica Argentina in 1981 and his Ph.D. in organic chemistry from the Universidad Nacional de Rosario in 1986. After a postdoctoral fellowship at the University of Pennsylvania with Prof. K. C. Nicolaou and later with Prof. Ralph Hirschmann from 1987 to 1990, he moved to Gif sur Yvette, France, as a research associate at the Institute de Chimie des Substances Naturelles. In 1992 he returned to the Universidad Nacional de Rosario, where he is now Professor of Organic Chemistry. His research encompasses interests in green chemistry, natural products synthesis, and development of new materials.



Scheme 3.

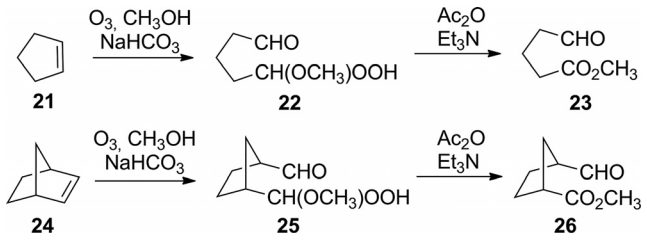
groups are obtained. Because the ester and the carbaldehyde (**20a**, **20b**) can easily be distinguished chemically, this strategy provides the potential for separate regioselective manipulation of each of these functional groups.



Scheme 4.

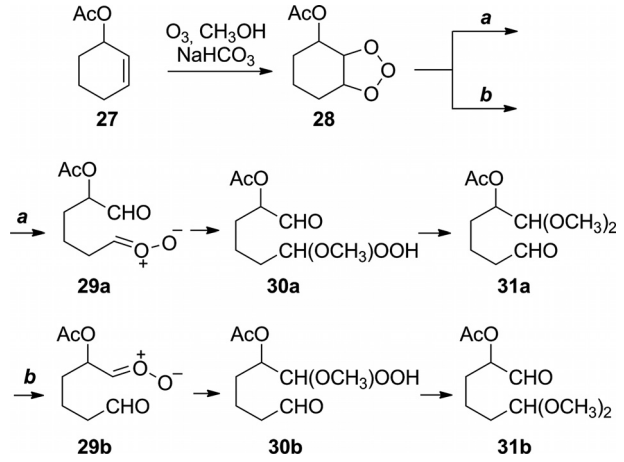
Discussion

Schreiber[6] was the first to recognize the advantage of ozonolytic cleavage of cycloalkenes in the presence of alcohols to afford different functional groups at each sp^2 carbon terminus. When the cyclic olefin is symmetrical (such as **21** or **24** in Scheme 5) the result is a single product with terminally differentiated end-like functional groups (such as **23** or **26**). However, when this reaction is applied to an unsymmetrical cycloalkene such as **27** (Scheme 6), two different products (**31a** and **31b**) can be obtained.



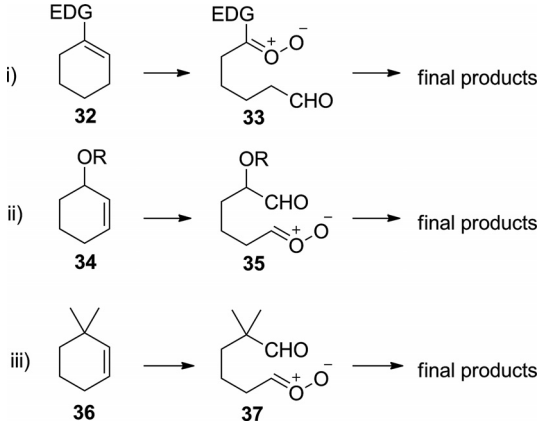
Scheme 5.

Both Schreiber and later authors initially referred to this process as "unsymmetrical ozonolysis", but this term is now considered ambiguous and confusing. For this reason the term "end-group-differentiating ozonolysis", as proposed originally by Carreira et al.,[7] is used throughout this review.



Scheme 6.

Because the final product is defined by the PO fragmentation, much of the current interest in this process centers on the factors that affect the direction of this cleavage. Intense research activity in recent years has clarified the effect on the fragmentation process of different types (or different numbers) of substituents attached to the sp^2 carbons.[8] The many examples reported in the literature have led to the understanding that at least three factors play an important role in determining the regiochemistry of the PO cleavage: i) the electronic nature of the substituent attached to the C–C double bond, ii) the electronic character of a heteroatom substituent at the allylic position, and iii) the steric effect of the allylic dialkyl substituent. When a substituent is attached directly to the double bond, as exemplified by **32** (Scheme 7), cleavage of the PO tends to occur by the pathway that places the electron-donating substituents on the carbonyl oxide fragment.[9] The carbonyl oxide **33** will hence be formed on the carbon with the substituents that are better suited to stabilize a developing positive charge.[10]



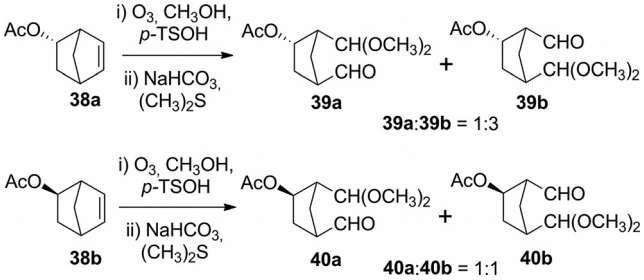
Scheme 7.

Literature reports[6,11,12] have indicated that simple inductive arguments reliably predict the electronic effect of a heteroatom substituent at the allylic position, as exemplified by the unsymmetrical cycloalkene **34** (Scheme 7).

The steric hindrance produced by the allylic dialkyl substituents in compound **36** (Scheme 7) plays an important role in the cycloreversion process of the PO, because it yields the carbonyl oxide product **37**, with the geminal dialkyl groups more remote from the carbonyl oxide fragment.[13]

Last but not least, remote factors have also been reported to influence the regioselectivity of PO fragmentation. These factors remain incompletely understood and represent an opportunity for both mechanistic and synthetic studies.

Schreiber's[6] report on the ozonolysis of the *endo*-5-norbornen-2-ol acetate **38a** (Scheme 8) offered the first example of an effect of a remote substituent on the regiochemical outcome of PO fragmentation. In the case of the *exo* isomer **38b**, the remote acetyloxy substituent failed to exert any control over the regiochemical outcome of the reaction. In contrast, reasonable regioselectivity was observed for the *endo* isomer **38a**.

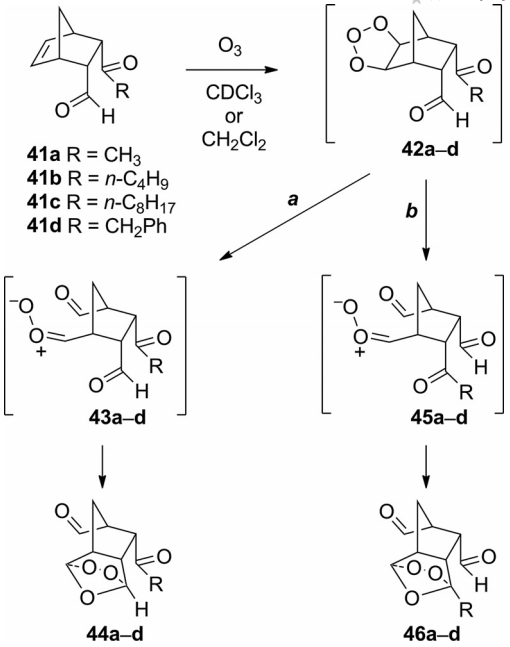


Scheme 8.

The preferred direction of cleavage of **38a** is the opposite of that predicted by consideration of the inductive effects of the acetyloxy substituent, so these results suggested that the cleavage of the PO was not governed by electronic effects arising from the distant acetoxy substituent.

The first observations of exclusive PO fragmentation controlled by different remote carbonyl groups and of stereoselective formation of final cross ozonides through the ozonolysis of norbornene derivatives were reported by Wu.[9,14]

Ozonolysis of the *endo* adducts **41a**–**d** (Scheme 9) gave the final ozonides **44a**–**d**, each as the sole product, in more than 95% yield.[9,14] A mechanism for the exclusive formation of the final ozonides **44a**–**d** from the ozonization of **41a**–**d** is outlined. 1,3-Dipolar cycloaddition of ozone to the *exo* faces of the alkene bonds of **41a**–**d** would give the 1,2,3-trioxolanes **42a**–**d**. According to Wu,[9] least-motion fragmentation of the 1,2,3-trioxolane rings in the primary ozonides **42a**–**d** is affected by the carbonyl groups and leads exclusively to the *syn*-oriented carbonyl oxides **43a**–**d**. Rapid intramolecular 1,3-dipolar cycloaddition between the *syn*-carbonyl oxide groups in **43a**–**d** and the *endo* formyl groups gives the final ozonides **44a**–**d** with *endo* stereochemistry. Because no detectable amounts of the isomeric final ozonides **46a**–**d** were found, formation of the isomeric carbonyl oxides **45a**–**d** from **42a**–**d** is excluded.



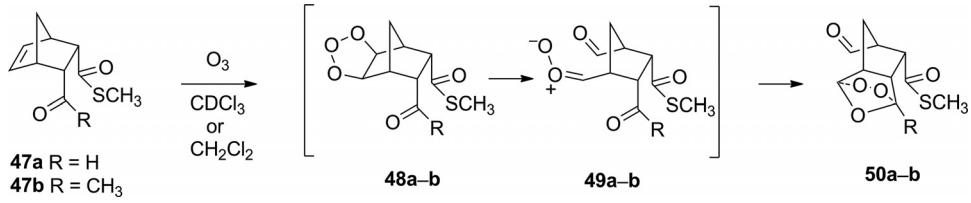
Scheme 9.

It was proposed that the exclusive regioselective fragmentation of the POs **42a**–**d** to form the carbonyl oxides **43a**–**d** was the result of a controlling influence exerted by the two different carbonyl groups. To account for these observations, the formyl group rather than the acyl group influences the space-closed trioxolane carbon to form the carbonyl oxide group. Because the formyl group and the acyl group are each three σ bonds distant from the PO ring, it was proposed[9] that the fragmentation of the trioxolane rings in **42a**–**d** is in each case induced by the *endo* formyl group in through-space rather than through-bond fashion, and that it is the oxygen atom of the formyl group rather than that of the acyl group that comes into proximity to the 1,2,3-trioxolane ring, providing anchimeric assistance.

In order to determine the relative abilities of a thioester group and a ketone (or aldehyde) group to control the fragmentation of a PO, compounds **47a** and **47b** (Scheme 10) were prepared.[9] Ozonolysis of **47a** and **47b** in $CDCl_3$ at –78 °C gave exclusively the final ozonides **50a** and **50b**, respectively. Again, no isomeric final ozonides were detected. With the assumption that a mechanism similar to that depicted in Scheme 9 is followed, the acetyl (or formyl) group rather than the thioester group influences the space-closed trioxolane carbon in **48a** (or **48b**) in such a way as to form the carbonyl oxide group,[9] probably through anchimeric assistance.

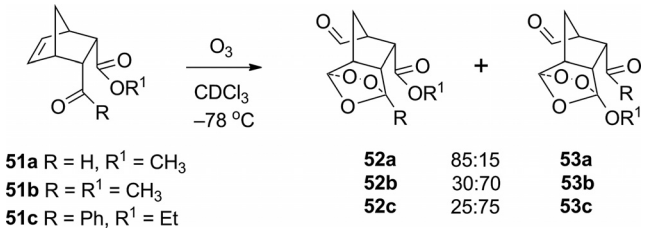
From these results, the order of preference of various carbonyl groups in exertion of through-space control of PO fragmentation in norbornene derivatives is aldehyde carbonyl > ketone carbonyl > thioester.

In a similar study, the ability of an ester group to control the fragmentation of a PO was compared to those of other carbonyl groups with the *endo* adducts **51a**–**c** (Scheme 11).[9] Compound **51a** gave the final ozonides **52a**



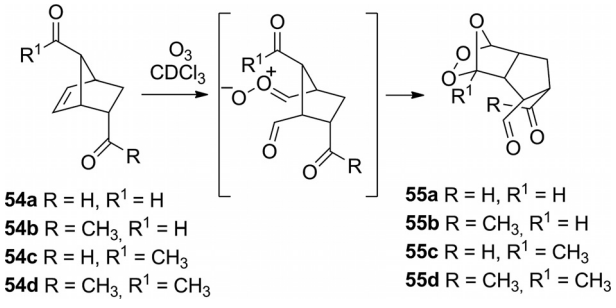
Scheme 10.

and **53a** in a ratio of 85:15, **51b** gave **52b** and **53b** in 30:70 ratio, and **51c** produced **52c** and **53c** in 25:75 ratio. These results suggest that the ability of an ester group to direct PO fragmentation towards the formation of a carbonyl oxide group is in between that of an aldehyde and that of a ketone carbonyl.



Scheme 11.

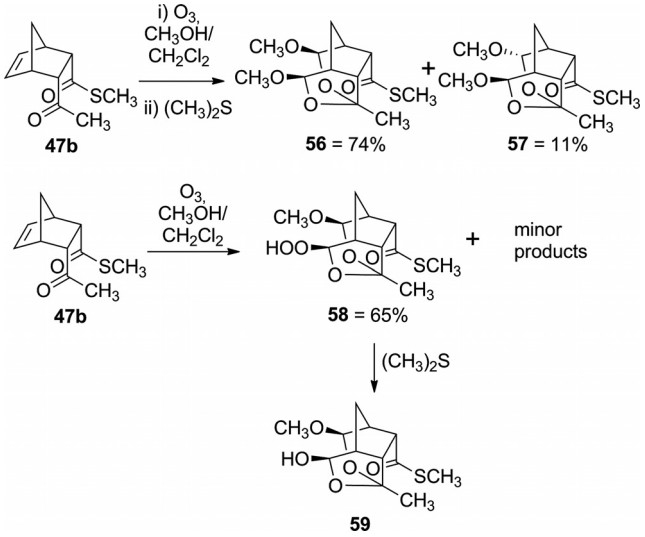
In a later publication, Wu and co-workers[14b] reported that ozonolysis of 2-*endo*-7-*anti*-diacylnorbornenes **54a**–**d** (Scheme 12) in deuterated chloroform at –78 °C afforded the final ozonides **55a**–**b** as sole products in more than 90% yields and **55c**–**d** as major products in approximately 80% yields. These data suggest that it is the *anti* carbonyl group on the apical carbon rather than the *endo* carbonyl group that reacts preferentially with the carbonyl oxide group to form the intramolecular cross ozonide.



Scheme 12.

The four examples in Scheme 12 all illustrate fragmentation with regioselectivity opposite to that seen for analogues lacking the apical acyl group.[9,14]

When the norbornene **47b** (Scheme 13), containing a thioester and a methyl ketone, is subjected to ozonolysis in CH_2Cl_2/MeOH at –78 °C, followed by reduction with Me_2S, compounds **56** and **57** are isolated in 74% and 11% yields, respectively. The structures of **56** and **57** were determined by X-ray analysis.[15]

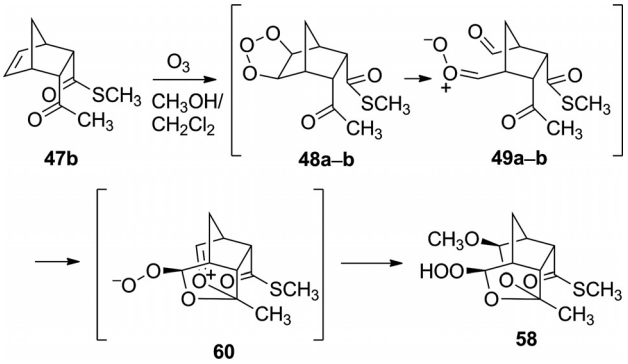


Scheme 13.

If the reaction is performed sequentially [that is to say, ozonolysis of **47b** in CH_2Cl_2/MeOH (1:1) at –78 °C without reduction], compound **58** is obtained as the major product (65%) with unidentified minor products. Subsequent reduction of **58** with dimethyl sulfide gives hemiacetal **59** (Scheme 13). If the thioester group of compound **47b** is replaced with an ester group, a similar result for the ozonolysis reaction is observed. In these ozonolysis reactions, neither the thioester nor the ester group participates in the intramolecular sequential nucleophilic addition.

On the other hand, as mentioned above. ozonolysis of **47b** in dichloromethane in the absence of methanol gave the final ozonide **50b**, via the intermediates **48b** and **49b** (Scheme 10).

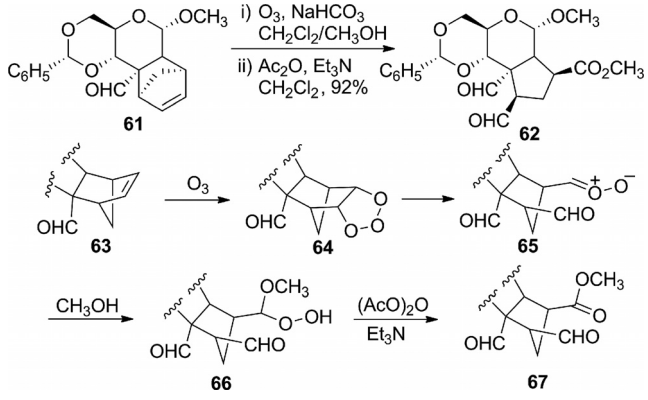
The proposed mechanism for the formation of compound **58** by ozonolysis of **47b** in CH_2Cl_2/MeOH cosolvents is shown in Scheme 14. The key factors are the regioselective rupture of the PO, assisted by the *endo* methyl ketone, and the intramolecular sequential nucleophilic addition of the carbonyl groups to the carbonyl oxide groups in **49a** and **49b**, which is faster than the intermolecular nucleophilic addition of a methanol molecule to the carbonyl oxide.



Scheme 14.

Wu's group's studies with different series of *endo*-substituted norbornene derivatives allowed them to propose that the fragmentation of the trioxolane ring was induced by the *endo* formyl group through space rather than through bond interaction, probably through anchimeric assistance.

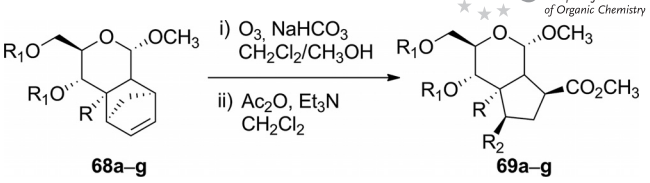
These reactions could find a wide variety of applications in organic synthesis if it were possible to control their regioselectivity so as to afford only one isomer instead of a mixture of the two possible ones. In a study on the synthesis of pentalenolactone,[16,17] end-group-differentiating ozonolysis of carbohydrate-derived norbornene system **61** (Scheme 15) showed an exceptionally high regioselectivity in the PO fragmentation. After workup, the polyfunctionalized cyclopentane **62** was the sole product, in 92% isolated yield.



Scheme 15.

This highly non-symmetric process is evidently controlled by substituents at least two carbon atoms distant from the double bond. A noteworthy observation is the fact that the carbonyl group attached at the quaternary center is in an *exo* position with respect to the olefin in this norbornene system.

In order to investigate the directing effects of other functional groups further, several analogues of **61** in which the aldehyde group was replaced by various functional groups with different steric and electronic demands were prepared.[18] The benzylidene acetal group was also removed in order to gain system flexibility and to evaluate how the rigidity affects the ozonolysis outcome (Scheme 16).



Scheme 16.

In each case the same regioselectivity was found, with only one of the two possible product regioisomers being isolated, in good to very good yields for compounds **69a**–**g**. The results in Table 1 show that the PO fragmentation is independent of the nature of the functional group attached at the quaternary carbon.

Table 1. Ozonolysis of *exo* norbornene systems.

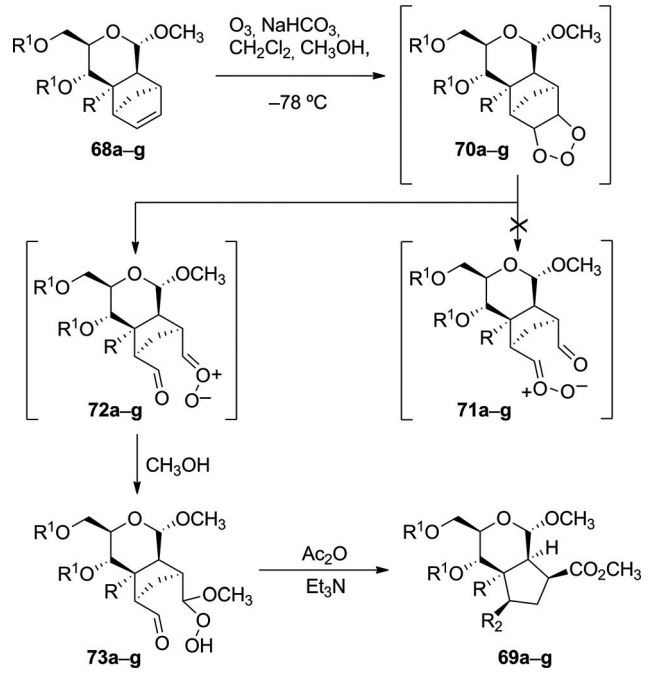
Entry	Starting material	R	R^1	R^2	Yield [%]
1	**68a**	CHO	benzylidene acetal	CHO	92
2	**68b**	CH_2OH	benzylidene acetal	CHO	69
3	**68c**	CO_2CH_3	benzylidene acetal	CHO	95
4	**68d**	$CH(OH)CH_2CH_3$[a]	benzylidene acetal	CHO	62
5	**68e**	$COCH_2CH_3$	benzylidene acetal	CHO	45
6	**68f**	CH_2OAc	benzylidene acetal	CHO	96
7	**68g**	CH_2OAc	acetate	=CHOAc[b]	86

[a] The configuration of the secondary alcohol was not determined. [b] The ozonolysis of the norbornene **68g** afforded the enol acetate derivative as the only product.

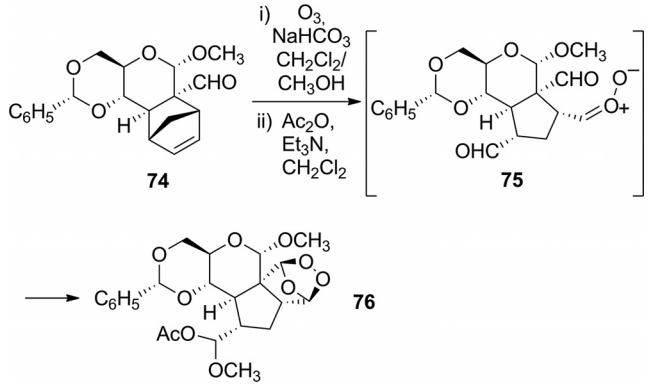
It was suggested that the major influence on the regioselectivity of the fragmentation of the PO is the quaternary center, and not any of the substituents (Scheme 17).

To test this hypothesis, new norbornene **74** (Scheme 18), with a substituent attached at the other ring fusion position, was synthesized.[18] In this case, the Diels–Alder cycloaddition gives only the *endo* isomer **74**. Two factors – the interaction of the *endo* carbonyl group through space and the influence of the quaternary carbon – might hence play a role in the end-group-differentiating ozonolysis. Ozonolysis of *endo* cycloadduct **74** afforded **76** (Scheme 18) as the only product (in 54% yield). Evidently in this example there is a high regioselectivity for the generation of the carbonyl oxide, with the carbonyl interaction through space being the dominating effect on the regioselective fragmentation of the PO. Once the carbonyl oxide is formed, as in the intermediate **75**, it is trapped by the neighboring aldehyde, which outcompetes the nucleophilic trapping of the methanol present in the medium. In addition, the free aldehyde is trapped as a mixed acetoxy/methoxy acetal.

Subsequently, the abilities of other functional groups to control the fragmentation of the POs in these systems were studied.[18]



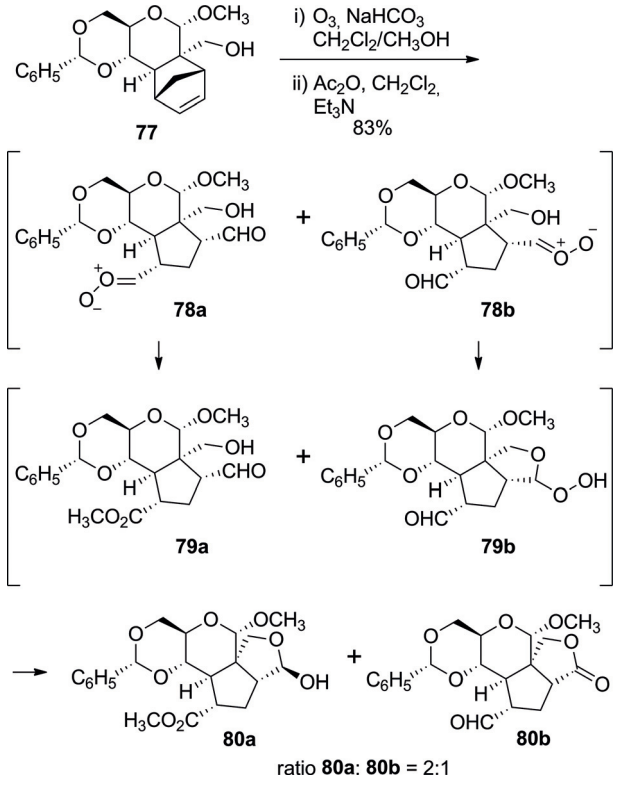
Scheme 17.



Scheme 18.

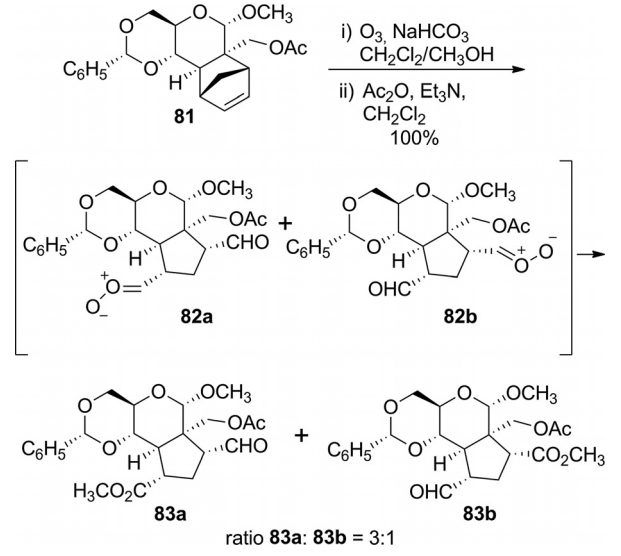
Ozonolysis of the primary alcohol **77** (Scheme 19) afforded a mixture of two products – **80a** and **80b** – in a ratio of 2:1. This example demonstrates that the ability of an alcohol group to control the PO fragmentation through space is lower than that of the aldehyde group, even though it could act as an intramolecular trapping agent of the carbonyl oxide once it is formed. Again, like in the previous series of compounds **68**, the major product is the regioisomer originating from the generation of the carbonyl oxide at the position more distant from the quaternary center. This means that the hydroxy directing group is outcompeted by the effect of the quaternary carbon.

The acetylated derivative **81** (Scheme 20) also yielded a mixture of two isomeric products – **83a** and **83b** – in a ratio of 3:1. This example makes it evident that the directing effect of an acetate group is lower than that of a hydroxy group, and significantly lower than that of an aldehyde group. According to these experiments, in this system the



Scheme 19.

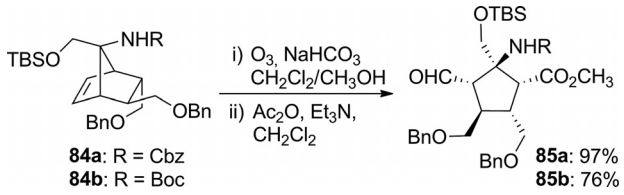
acetate and hydroxy directing groups are both outcompeted by the effect of the quaternary carbon, whereas the quaternary carbon is not a competitor to the aldehyde group.



Scheme 20.

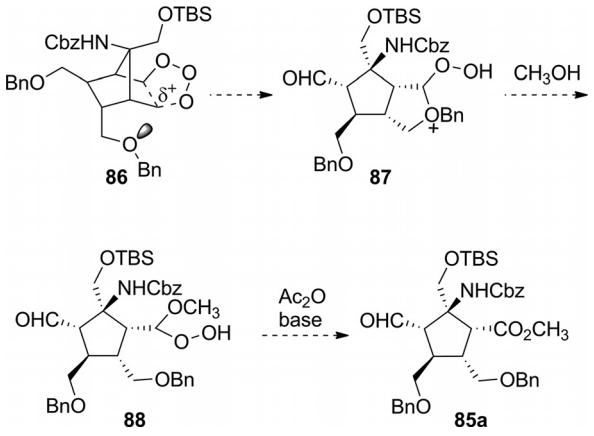
More recently, Carreira's group published a series of three contributions relating to the enantioselective synthesis of fragments of massadine, in which regioselective ozonolytic end-group differentiation cleavage of a norbornene skeleton was used as the key reaction.[7,19,20] In their first example, they reported that ozonolytic cleavage of the nor-

bornene **84a** (Scheme 21) distinguished between the two sp^2-hybridized carbons. This transformation proved to be robust, even on a multigram scale.



Scheme 21.

They hypothesized that the presence of the *endo*-oriented benzyloxy group is crucial for the selective breakdown of the primary ozonide **86** (Scheme 22), possibly through the formation of hydroperoxide intermediate **87**.



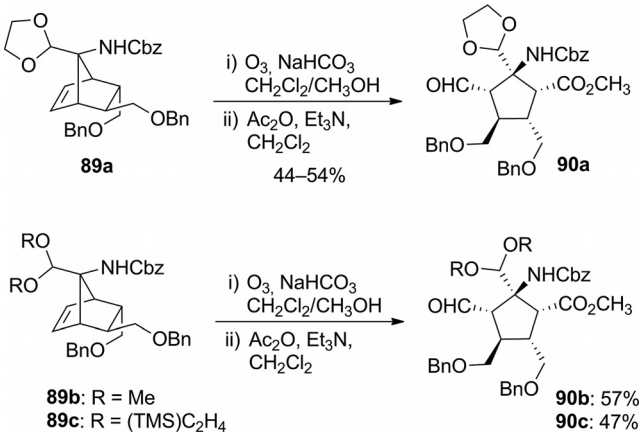
Scheme 22.

The observed end-group differentiation is notable because it provides a tactical solution to the selective manipulation of the norbornene skeleton. Additionally, it is remarkable that the end-group differentiation occurs in the absence of strong inductive effects operating at the ends of the olefin.

In the second contribution of this series, Carreira et al. reported that ozonolysis of **84b** (Scheme 21, Boc-protected analogue of **84a**) gave cyclopentane **85b** in 76% yield.[19]

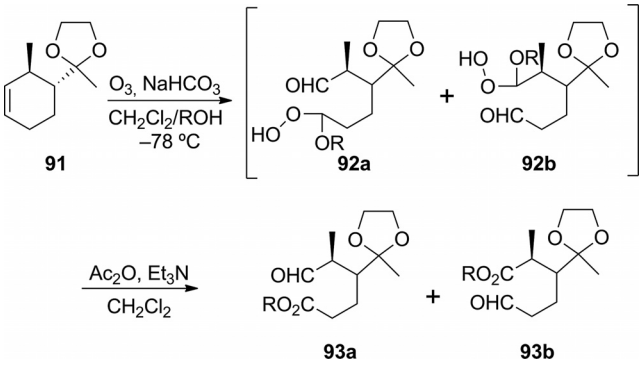
In their final publication of the series, they highlighted end-group-differentiating ozonolysis as a key step in their approach towards the synthesis of massadine.

They subjected the acetal **89a** (Scheme 23) to the ozonolytic cleavage conditions to isolate the ester/aldehyde **90a** as the only isomer, in yields ranging from 44 to 54%.[20] This transformation suffered from undesired side reactions, predominantly during the second stage of the sequence. Despite different attempts to suppress the substrate loss by changing the reaction time and temperature, the overall yield could not be improved. Application of this two-step sequence to dimethyl- and bis(trimethylsilyl)ethyl acetal analogues **89b** and **89c** resulted in the regioselective formation of ester/aldehydes **90b** and **90c** in 57 and 47% yields, respectively (Scheme 23). Substantial product decomposition, like that seen with the previous example of ester aldehyde **90a**, was also observed during these experiments. The best results were obtained with norbornene **84a**.



Scheme 23.

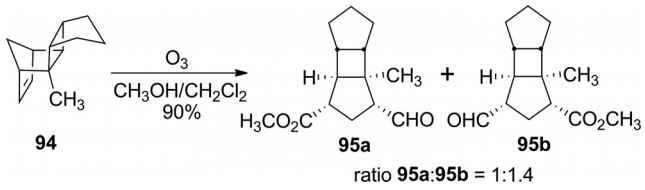
An example of the ozonolytic cleavage of an unsymmetrical cyclohexene was reported by Taber et al. in 2001.[21] Although this outstanding paper did not involve a norbornene skeleton, it nevertheless deserves mention because it has inspired other chemists to try reactions of this kind in different systems. Upon end-group-differentiating ozonolysis, ketal derivative **91** (Scheme 24) afforded **93a** and **93b** as an inseparable mixture. It is important to note that in this case there are two directing effects: the methyl group in the allylic position and the through-space effect of the dioxolane group. Additionally, the authors briefly explored the use of other alcohols in the solvent mixture. In methanol, ethanol, and propan-2-ol the ratio of **93a** to **93b** was 3.6:1 (68–73% yield). In benzyl alcohol this ratio was increased to 4.8:1 (75% yield), and in *tert*-butyl alcohol to 6.0:1 (48% yield). Although *tert*-butyl alcohol appeared to enhance the regioselectivity of the reaction pathway, the authors suggested that the lower yield obtained might be due to selective loss of the minor regioisomer.



Scheme 24.

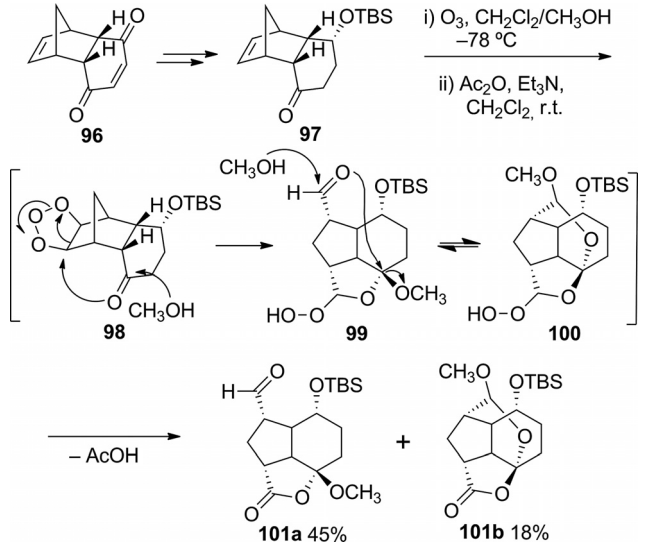
In another report, relating to the synthesis of cyclobutane-containing natural products, Harmata ozonized the norbornene system **94** (Scheme 25) by the protocol introduced by Schreiber and co-workers. This procedure afforded the two regioisomeric ester aldehydes **95a** and **95b**

in 90% overall yield in a ratio of 1:1.4.[22] In this case (and consistently with Wu's proposal), there is a slight influence of the *endo* methyl group as a weak director of the PO fragmentation, thus barely favoring formation of compound **95b**.



Scheme 25.

During the course of their studies directed towards otteliones, Metha and Islam took advantage of end-group-differentiating ozonolysis of a norbornene-type cycloadduct to obtain a mixture of two isomers, both arising from the same regioselective ozonide fragmentation (Scheme 26).[23]



Scheme 26.

The regioselectivity observed during the end-group-differentiating ozonolysis leading to the formation of **101a** and **101b** was explained by the authors in terms of assisted intramolecular cleavage of the primary ozonide as in **98**, followed by the participation of intermediates **99** and **100**, respectively. This outcome agrees with Wu's proposal and shows that the ability of an *endo* ketone to direct PO fragmentation towards the formation of a carbonyl oxide group is greater than that of an *endo* alcohol protected as the *tert*-butyldimethylsilyl ether.

Conclusions

The effects i) of a substituent on the C=C double bond, ii) of a heteroatom at the allylic position, and iii) of an allylic dialkyl substituent on the selective breakdown of a PO are well understood. In the case of a norbornene with an *endo* substituent there is induction of the group in through-space fashion or anchimeric assistance that places the carbonyl oxide on the same side as the controlling group. Subsequent transformations will determine the structure of the final product. In the ozonolysis of norbornene derivatives, the abilities of various remote carbonyl groups in the *endo* position to control the fragmentation of the PO in through-space fashion are as follows: aldehyde carbonyl > ketone carbonyl > thioester. The strength of an aldehyde as a controlling group relative to other non-carbonyl groups is as follows: aldehyde carbonyl > alkyl alcohol > acetylated or silylated alcohol. As a consequence of this experimentally determined tendency, the regioselective fragmentation of the PO of a norbornene with a controlling group in an *endo* position can easily be predicted except when there is a quaternary carbon, which outcompetes the directing effect of the functional groups mentioned.

When the remote controlling group in a norbornene system is in an *exo* position, that group has little or negligible influence on the PO rupture. If this group is located at a quaternary carbon, however, this highly substituted center can have a major influence on the regioselective fragmentation of the PO. In this case, the regiochemistry of the PO rupture will not be easily predictable.

From the mechanistic point of view, it will require more time and research to gain deeper understanding of the process controlling the selective breakdown of the PO.

End-group-differentiating ozonolysis of norbornenes is a useful tool for the construction of highly substituted cyclopentanes. Conformationally rigid norbornenes could thus be seen as reliable precursors for complex cyclopentane systems. Moreover, appropriately functionalized norbornenes can be obtained through stereoselective Diels–Alder cycloaddition, which makes this sequence an attractive general strategy.

It is to be expected that end-group-differentiating ozonolysis of norbornenes will come to be used increasingly, given its utility and robustness. The guidelines given in this review should aid better understanding of end-group-differentiating ozonolysis and make more chemists willing to use it in their synthetic endeavors. Hopefully in this way more examples will be made available and will help to unveil the factors that are not yet completely understood.

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