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THE FIRST EXCLUSIVE REGIOSELECTIVE FRAGMENTATION OF PRIMARY OZONIDES CONTROLLED BY REMOTE CARBONYL GROUPS

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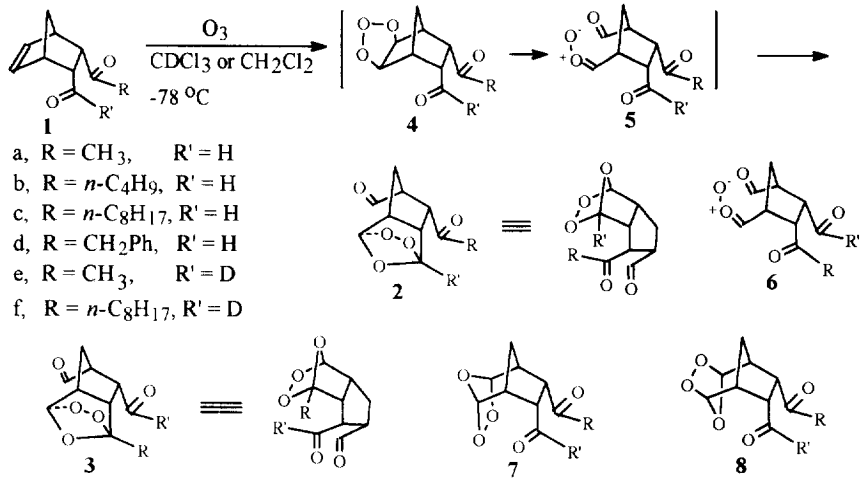
Abstract: Ozonolysis of compounds **1a-1d** in $CDCl_3$ at -78 °C regioselectively and stereoselectively gave the corresponding final ozonides **2a-2d** as the sole product, which, after treatment with triethylamine, gave the novel convex tetraquinane oxa-cages **9a-9d** in high yields respectively.

Extensive investigation of the mechanism of alkene ozonolysis has confirmed the essential features of the pathway originally proposed by Criegee.[1] Substituent effects on the regioselectivity of primary ozonides (PO) fragmentation have been reported in the cases that the subtituents are directly placed on the alkene bond.[2] The cleavage of PO tends to occur along the path which results in the placement of electron-donating substituents on the carbonyl oxide fragment, while electron-withdrawing substituents are incorporated in the carbonyl product. To our knowledge, the regioselective fragmentation of PO controlled by remote carbonyl groups has not yet been demonstrated.[3] We report here the first observation of exclusive regioselective fragmentation of primary ozonides and stereoselective formation of final ozonides controlled by remote different carbonyl groups on ozonolysis of norbornene derivatives.

Ozonolysis of **1a-1d** in $CDCl_3$ at -78 °C gave the final ozonides **2a-2d** as the sole product (>95%) respectively, Scheme 1. The ^1H and ^{13}C nmr spectra of **2a-2d** were taken at -30 °C right after the ozonation process without purification. No detectable amount of the isomeric final ozonides **3a-3d** was observed from the ^1H and ^{13}C nmr spectra of the crude products of the ozonation of compounds **1a-1d**. The ^1H nmr spectrum of **2a** reveals two singlets at δ 6.45 and 5.70 for the ozonide ring protons and a singlet at δ 2.21 for the methyl ketone protons,

consistent with structure **2a** rather than **3a**. The ^{13}C nmr spectrum of **2a** shows two peaks (CH) at δ 103.7 and 101.6 for the two tertiary bridgehead carbons of the ozonide ring indicating no quaternary carbon present at the ozonide ring bridgehead. Ozonolysis of the deuterated compounds **1e** and **1f** in $CDCl_3$ at -78 °C gave the final ozonides **2e** and **2f** as the sole product (>95%) respectively. No detectable amount of the isomeric final ozonides **3e** and **3f** was observed. The crude ^1H nmr spectra of **2e** and **2f** reveal that the deuterium atom locates on the bridgehead of the trioxolane ring of **2e** and **2f**. Thus, these experiments rule out the possibility of the structure of the final ozonides to be **7** or **8**.

Scheme 1

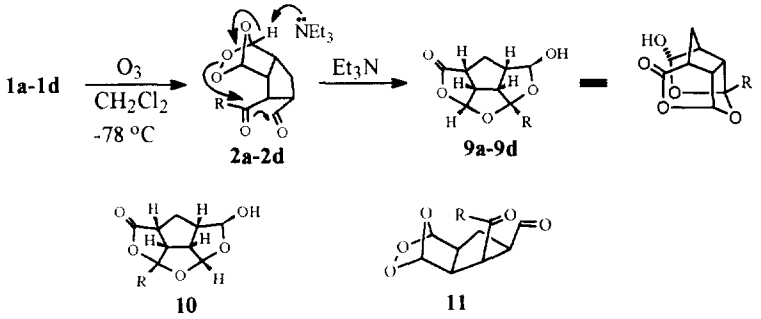


A mechanism is proposed for the exclusive formation of the final ozonides **2** from the ozonation of **1**, Scheme 1. 1,3-Dipolar cycloaddition of an ozone molecule with the alkene bond of **1** via *exo* face gave the 1,2,3-trioxolanes **4**. A least-motion fragmentation[4] of the 1,2,3-trioxolane ring of the primary ozonides **4** affected by the carbonyl groups led exclusively to the *syn*-oriented carbonyl oxides **5**. Rapid intramolecular 1,3-dipolar cycloaddition of the *syn* carbonyl oxide group of **5** with the *endo* formyl group gave the final ozonides **2** with *endo* stereochemistry. Since no detectable amount of the isomeric final ozonides **3** was obtained, formation of the isomeric carbonyl oxides **6** from **4** would be excluded. The exclusively regioselective fragmentation of the primary ozonides **4** to form the carbonyl oxides **5** is controlled by the two different carbonyl groups. According to the above results, it is the formyl group rather than the acyl group to induce the space-closed trioxolane carbon to form the carbonyl oxide group. If the fragmentation of the primary ozonides **4** was not preferentially

controlled by the *endo* formyl group, both the carbonyl oxides **5** and **6** should be formed. Consequently, both the final ozonides **2** and **3** should be obtained. Since both the formyl group and the acyl group are three σ bonds remote to the primary ozonide ring, we propose here that the fragmentation of the trioxolane ring of **4** is induced by the *endo* formyl group through space rather than through bond and that it is the oxygen atom of the formyl group rather than the oxygen atom of the acyl group to adopt a conformation in proximity to the 1,2,3-trioxolane ring of **4**.

Ozonolysis of **1a-1d** in dichloromethane at -78 °C followed by reaction with triethylamine regioselectively gave the convex tetraquinane oxa-cage compounds **9a-9d** in 80-85% yields respectively, Scheme 3. No detectable amount of the other regioisomers **10a-10d** was obtained in each case. These results indicate that ozonolysis of **1a-1d** in CH_2Cl_2 or $CDCl_3$ at -78 °C exclusively gives the corresponding final ozonides **2a-2d** which, in reaction with triethylamine, give **9a-9d** as the sole product respectively. The regiochemistry of the angular alkyl groups of **9a-9d** was assigned by H-H COSY 2D spectral analysis. A mechanism is proposed for formation of **9** from **2**, Scheme 2. Proton abstraction of the trioxolane ring proton of **2** by triethylamine followed by heterolytic cleavage of the peroxide bond and sequential nucleophilic addition of the newly-formed alkoxide ions to the adjacent carbonyl groups gave the sole product **9**. If both the isomeric final ozonides **2** and **3** were formed from ozonolysis of **1**, both isomeric compounds **9** and **10** should be obtained via reaction of triethylamine with **2** and **3**. Thus, these experimental results support the observation described in Scheme 1.

Scheme 2

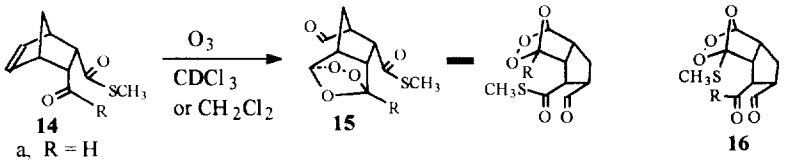


The final ozonides formed by ozonolysis of **1a-1d** in CH_2Cl_2 or $CDCl_3$ at -78 °C is deduced to be the *endo* isomer **2** instead of the *exo* isomer **11**. If the final ozonides were the isomers **11a-11d**, with an *exo* stereochemistry, proton abstraction of the trioxolane ring proton of **11** by triethylamine followed by heterolytic cleavage of the peroxide bond could not give the observed

products **9a-9d** since the sequential nucleophilic addition of the newly-formed alkoxide ions to the carbonyl groups is stereochemically impossible.

Ozonolysis of **14a** and **14b** in $CDCl_3$ at -78 °C exclusively gave the final ozonides **15a** and **15b** respectively, Scheme 3. Again, no detectable amount of the isomeric final ozonides **16a** and **16b** was observed from the ^1H and ^{13}C nmr spectra of the crude products of the ozonation of compouns **14a** and **14b**.

Scheme 3



14
a, R = H
b, R = CH_3

15

16

Thus, the order of the preference of various carbonyl groups to control through space the fragmentation of the primary ozonides formed by ozonolysis of norbornene derivatives is as follow: aldehyde carbonyl > ketone carbonyl > thioester. The ability of ester and amide groups to control the fragmentation of the primary ozonides needs to be discovered.

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