Synthesis of a functionalized furan via ozonolysis—further confirmation of the Criegee mechanism

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ABSTRACT

A new method for the synthesis of a tetrahydrofuran ring is described which involves ozonolysis of a diene possessing a free hydroxy group in the γ-position. The reaction proceeds via ozone attack on the terminal double bond, cleavage, and intramolecular cyclization through the free hydroxy group. The cyclization event can be rationalized through formation of Criegee's carbonyl oxide, but not through the 'unified' mechanism, thereby lending support to the Criegee mechanism as a method of producing oxygen-containing heterocycles.

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Oxygen-containing heterocycles are structural motifs widely found in natural products of different origins. A range of biologically active compounds such as C-nucleosides, ionophore antibiotics, acetogenins, and brevetoxins incorporate cyclic polyether moieties in their structural backbone. Consequently, considerable effort has been undertaken to elaborate new and efficient synthetic methods to access cyclic ethers of different ring sizes.[1] Functionalized polyethers are of particular interest in synthetic organic methodology, because their synthesis often requires considerable effort.

Historically, different strategies have been undertaken in order to access functionalized O-heterocycles. The most common strategy is based on a biomimetic approach and consists of assembling the specifically functionalized aliphatic chain, followed by a C–O cyclization reaction, promoted by different electrophilic or radical initiators.[1] Typically, the formation of cyclic ethers is a two-step process involving the formation of a carbocation through electrophilic addition to an olefin, followed by intramolecular nucleophilic attack of an oxygen substituent on the carbocation (Scheme 1). This strategy works well for the synthesis of tetrahydrofuran ring systems. On the other hand, the utility of a conjugated diene system in such a transformation is under explored. In our opinion, the conjugated system can contribute to an alternative reaction course and may result in greater flexibility for building functionalized oxygen heterocycles.

Research on the isolation of polyethers from the marine dinoflagellate Karenia brevis has delivered various families of ladder frame polyethers containing conjugated dienes.[2] We envisioned that this functionality could be used for further functionalization of natural ladder frame polyethers.

In order to check the feasibility of this approach, we designed a model compound to mimic the lateral chain with conjugated double bonds that incorporates a free hydroxy group at the γ-position with respect to the olefinic bond. Based on the general mechanism of tetrahydrofuran formation (Scheme 1), one can assume that the generation of a carbonium ion in the lateral chain would inevitably lead to a cyclization event involving the free hydroxy group to provide a functionalized furan ring. The synthesis of the model substrate 1 is presented in Scheme 2.[3] The bicyclic system of 1 possesses a conjugated double bond in an equatorial position and a tertiary hydroxy group trans-configured relative to the lateral chain. It is noteworthy that an isoprenoid polycycle has recently been used as a model to support an alternative mechanism for the synthesis of marine polyether toxins.[4]

Functionalization of conjugated double bonds can be performed by selective ozonolysis, and this type of transformation is well documented for similar substrates.[5,6] In particular, it was demonstrated that the ozonolysis of conjugated double bonds proceeds
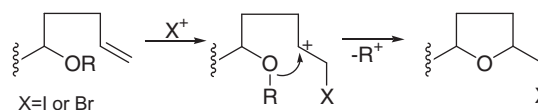
Scheme 1. Formation of tetrahydrofurans through carbocation generation.

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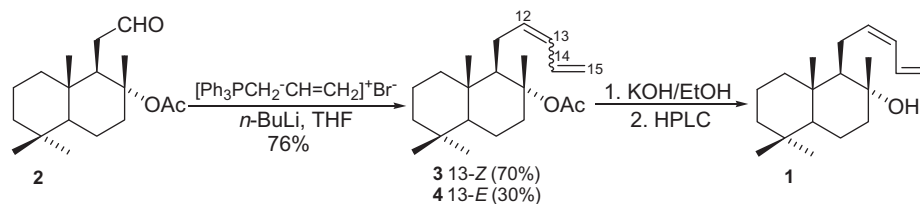
Scheme 2. Synthesis of model substrate **1**.
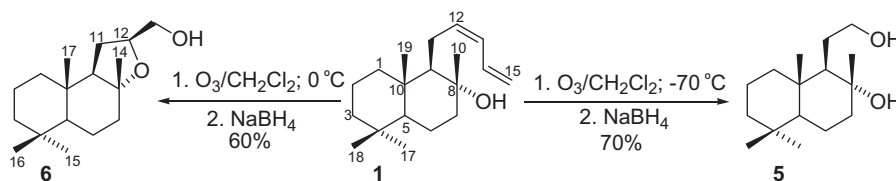
Scheme 3. Ozonolysis reactions of **1**.
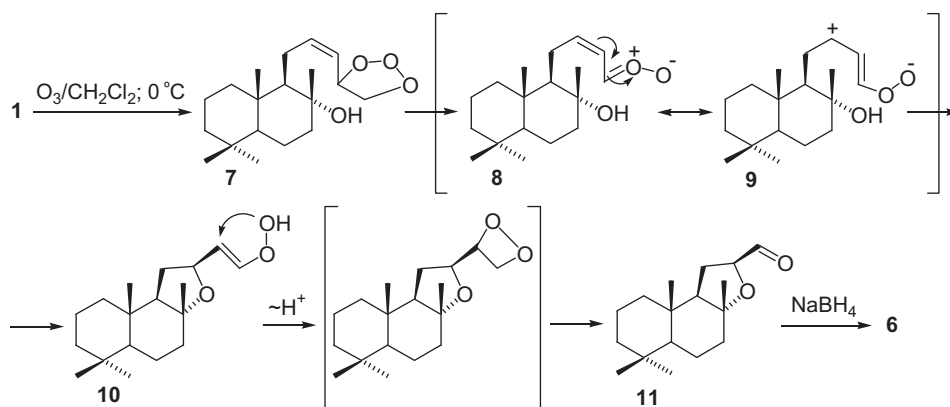
Scheme 4. Proposed mechanism for the synthesis of tetrahydrofuran **6**.

sequentially,[5] and we also planned to transform selectively the lateral chain of **1** under different ozonolysis conditions.

Following these hypotheses, alcohol **1** was submitted to ozonolysis (Scheme 3). Ozone was added in slight excess and the reaction was performed at different temperatures. At −70 °C, the major product, after borohydride reduction, was the known diol **5**—a product of C12–C13 double bond cleavage. Performing the ozonolysis at 0 °C provided a compound containing two carbon atoms less than the initial diene side-chain suggesting cleavage of the C13–C14 bond.[7] The structure of this compound was determined as **6** using 1D and 2D NMR experiments.

The formation of alcohol **6** was quite unexpected, but the reaction course can be explained on the basis of the Criegee mechanism.[8] It is well known that this mechanism was the subject of controversial discussions and the most relevant alternative is the so-called unified concept.[9]

Recent work on this subject, employing labeled atoms,[10] has shown the viability of the Criegee scheme. Our current work brings further experimental evidence for this conclusion. In fact, the formation of alcohol **6** is only possible via Criegee's carbonyl oxide **8** (Scheme 4). Its stabilization by conjugation with the adjacent double bond leads to a partial positive charge at C12, intramolecular attack by the hydroxy group then forms the corresponding heterocycle **10**. Since the stability of the formed vinylic hydroperoxide is extremely low,[11] it decomposes to the aldehyde **11**, (possibly via a strained four-membered cyclic peroxide) which is reduced with

sodium borohydride to form the alcohol **6**. Similar 'abnormal' ozonolysis has been reported and explained on the basis of the intramolecular involvement of the free hydroxy group during the reaction.[12]

Tetrahydrofurans similar in structure to alcohol **6** are well known but their formation was based on a different mechanism, suggested on the basis of involvement of iodine in the reaction sequences.[13] From a synthetic point of view, the presence of the hydroxymethylene group at C12 in alcohol **6** represents an alternative opportunity for further functionalization.

In summary, a new method for the synthesis of tetrahydrofurans has been demonstrated. The procedure based on a tandem ozonolysis-cyclization reaction provides a good yield of the heterocyclic compound, possessing a lateral chain for further functionalization. To the best of our knowledge, this is the first example of ozonolysis of a conjugated diene with simultaneous cyclization, through utilization of an appropriately positioned hydroxy group, to prepare oxygen-containing heterocycles. The practical utility of the newly synthesized compound is currently under investigation.

References and notes

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3. Compounds **3** and **4**. Triphenylphosphonium allyl bromide (2.20 g, 5.72 mmol) was suspended in 15 mL of dry THF and treated with 3.5 mL of *n*-BuLi solution in hexanes (1.6 M, 5.72 mmol) at 0 °C under argon. The obtained solution was gradually warmed to room temperature over 30 min, then cooled to −30 °C, and a solution of 561 mg (1.91 mmol) of **2**[14] in 12 mL of THF was added dropwise. Stirring was continued at rt for 2 h, after which TLC analysis showed no remaining starting material. Diluting the reaction mixture with H_2O (50 mL) was followed by work-up, consisting of extraction with Et_2O (3 × 25 ml) and washing the organic phase successively with dilute H_2SO_4, saturated sodium bicarbonate solution, and brine to bring the pH to neutral. Drying over anhydrous Na_2SO_4 and evaporation of the solvent under reduced pressure gave the crude product which was submitted to column chromatography over silica gel. Elution with 5% EtOAc in petroleum ether gave 400 mg of a mixture of **3** and **4** as an oil, in a 7:3 ratio. ^1H NMR (500 MHz, $CDCl_3$, selected): δ_H = 0.807 (s), 0.811 (s), 0.87 (s), 0.89 (s), 0.90 (s)—all 9H; 1.48 (s), 1.50 (s)—all 3H; 1.91 (s), 1.92 (s)—all 3H; 4.94 (d, *J* = 10 Hz, 0.4H); 5.07 (d, *J* = 10 Hz, 0.4H), 5.09 (d, *J* = 16.5 Hz, 0.6H); 5.18 (d, *J* = 16.5 Hz, 0.6H); 5.51 (m, 0.6H); 5.75 (m, 0.4H); 5.91 (t, *J* = 11 Hz, 0.6H); 6.01 (dd, *J* = 10, 15 Hz, 0.4H); 6.31 (dt, *J* = 10, 17 Hz, 0.4H); 6.73 (dt, *J* = 10, 17 Hz, 0.6H). IR (cm^{-1}): 1250; 1728; 2933. A mixture of **3** and **4** (260 mg, 0.82 mmol) was treated with a solution of KOH (448 mg, 8 mmol) in EtOH (5 mL) for 2 h at gentle reflux. Dilution with H_2O and usual work-up gave a mixture of **1** and its corresponding *E*-isomer. This mixture was submitted to HPLC separation on a Phenomenex Luna 5 μm C18 semi-preparative column (9:1 MeOH–H_2O) to provide pure **1** (yellow liquid). ^1H NMR (500 MHz, $CDCl_3$): δ_H = 0.81 (s, 3H); 0.86 (s, 3H); 0.88 (s, 3H); 0.91–0.99 (m, 2H); 1.16 (m, 1H); 1.20 (s, 3H); 1.23–1.49 (m, 5H); 1.51–1.75 (m, 4H); 1.87 (m, 1H); 2.25 (m, 1H); 2.46 (m, 1H); 5.13 (d, *J* = 10 Hz, 1H); 5.21 (d, *J* = 17 Hz, 1H); 5.61 (m, 1H); 5.96 (t, *J* = 11 Hz, 1H); 6.77 (dt, *J* = 6, 5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 15.61 (C17); 18.78 (C2); 20.53 (C1); 21.77 (C18); 23.84 (C11); 24.54 (C16); 33.49 (C4); 33.67 (C19); 36.53 (C10); 40.42 (C6); 42.05 (C7); 44.38 (C3); 56.31 (C5); 62.42 (C9); 74.39 (C8); 117.35 (C15); 128.04 (C13); 132.37 (C14); 135.79 (C12). IR (cm^{-1}): 598; 903; 1122; 1387; 1462; 2928; 3336.

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7. Preparation of **6**. Diene **1** (10 mg, 0.036 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and treated with 1.5 mL of a saturated O_3 solution in CH_2Cl_2 at 0 °C for 10 min. Removal of excess O_3 with a stream of argon was followed by addition of excess $NaBH_4$ and stirring was continued at rt for 2 h. Dilution with H_2O and usual work-up (see Ref. 3) gave the crude product which was submitted to column chromatography over silica gel. Elution with 25% EtOAc in petroleum ether gave 6 mg of **6** (yellow liquid). ^1H NMR (500 MHz, $CDCl_3$): δ_H = 0.84 (s, 3H); 0.85 (s, 3H); 0.88 (s, 3H); 0.95–1.10 (m, 3H); 1.16 (s, 3H); 1.30 (m, 1H); 1.40–1.60 (m, 6H); 1.70–1.77 (m, 3H); 1.95 (m, 1H); 3.56 (dd, *J* = 7.5, 15 Hz, 1H); 3.67 (dd, *J* = 3.5, 10 Hz, 1H); 4.15 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 15.73 (C17); 18.61 (C2); 21.12 (C1); 21.24 (C15); 25.07 (C14); 25.41 (C11); 33.30 (C4); 33.72 (C16); 36.53 (C10); 40.20 (C7); 40.60 (C6); 42.65 (C3); 57.28 (C5); 60.90 (C9); 67.20 (C13); 79.30 (C12); 81.10 (C8). IR (cm^{-1}): 827; 912; 1009; 1376; 2921; 3430.

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