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Trisequential Photooxygenation Reaction: Application to the Synthesis of Carbasugars

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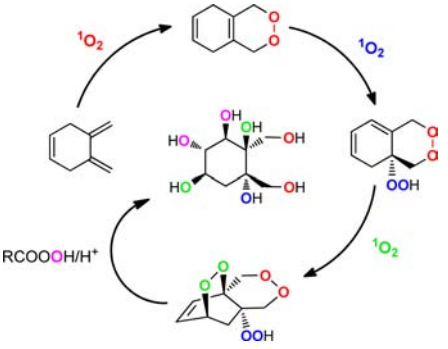
ABSTRACT



4,5-Dimethylenecyclohex-1-ene was subjected to a photooxygenation reaction to introduce oxygen functionalities. The endoperoxide obtained underwent an ene-reaction to form hydroperoxides with 1,3-diene structures. Further addition of singlet oxygen to the diene units resulted in the formation of tricyclic hydroperoxides having three oxygens in the molecule. Cleavage of the oxygen−oxygen bonds followed by epoxidation of the remaining C−C double bond and concomitant ring-opening reaction furnished the isomeric carbasugars.

Structural entities having polyhydroxylated cyclohexanoid cores are widely distributed in nature, and they have, in recent decades, attracted interest among chemists due to their significant biological properties and diverse synthetic intermediates.[1] Cyclitols are involved in glycosidase inhibition, intercellular communication, phosphate storage, protein anchoring, etc. Therefore, glycosidase inhibitors are generally regarded as promising candidates for the development of new drugs. Carbasugars,[2] generated by replacing the endocyclic oxygen atom in monosaccharides, are thought to be more viable drug candidates than natural sugars, since they are stable under hydrolytic conditions.[3]

Recently, we synthesized some new carbasugar derivatives[4] and showed that they inhibit the activity of α-glycosidase and increase the activity of α-amylase. Furthermore, we prepared various branched Carbahexopyranose derivatives, which showed strong inhibition for α-glycosidase.[5] Here, we describe the synthesis of new

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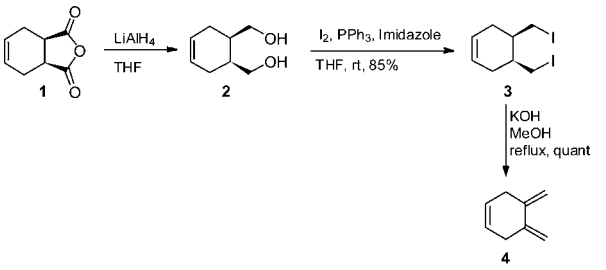
Scheme 1. Synthesis of the Diene **4**

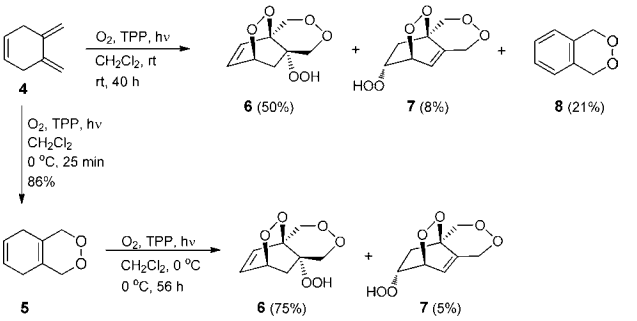


branched carbasugars where we applied a tandem reaction of singlet oxygen to 4,5-dimethylenecyclohex-1-ene (**4**).

The starting material, 4,5-dimethylenecyclohex-1-ene (**4**), was synthesized in four steps starting with the addition of maleic anhydride to in situ generated butadiene (Scheme 1). Reduction of **1**[6] with $LiAlH_4$ in THF afforded the diol **2**,[7] whose OH groups were iodinated with I_2, in the presence of imidazole and PPh_3 to give **3**.[8] The diiodide **3** was subjected to an elimination reaction of 2 mol of HI with KOH in methanol to afford the diene **4**[9] in almost quantitative yield.

Our route to carbasugars was based on a photooxygenation reaction of the diene **4** (Scheme 2). Photooxygenation[10] of diene **4** in methylene chloride (500 W, projection lamp, 25 min) at 0 °C using tetraphenylporphyrin as a sensitizer afforded the endoperoxide **5** in 86% yield. However, when the reaction was carried out at rt for 40 h, the reaction proceeded further and the endoperoxide **5** formed initially underwent a cascade photooxygenation reaction to form two regioisomeric tricyclic bis-endoperoxides **6** (50%) and **7** (8%) beside the aromatization product **8**[11] (21%). The products were separated by column chromatography.

Scheme 2. Synthesis of the Bis-endoperoxides **6** and **7**



The structures of **6** and **7** were assigned by ^1H and ^{13}C NMR spectra. The 300 MHz ^1H NMR spectrum of **6** in $CDCl_3$ exhibits two doublet of doublets at δ 6.83 (J = 8.5 and 6.1 Hz) and δ 6.18 (J = 8.5 and 1.5 Hz). The main coupling (8.5 Hz) is in agreement with the *cis*-configuration of the double bond protons. Further splittings arise from coupling with the bridgehead proton H-7. The methylene protons next to the hydroperoxide group resonate as an AB-system at δ 2.08 and δ 1.94 ppm. Both parts of this system show further coupling with the bridge-head proton H-7. The structure of the regioisomer **7** was established by NMR data. Further confirmation was achieved by single crystal X-ray analysis (Figure 1). The molecule **7** crystallized in the monoclinic space group $P2_1/n$ with Z = 4.

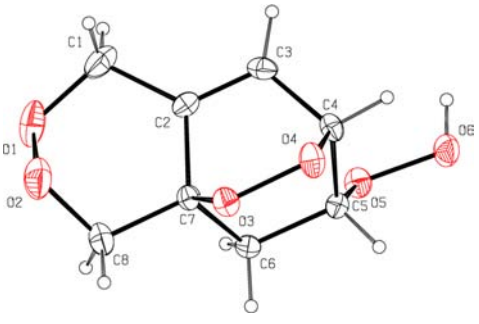


Figure 1. ORTEP diagram of **7**. Thermal ellipsoids are shown at 40% probability level.

For the formation of these bis-endoperoxides **6** and **7**, we suggest the following mechanism (Scheme 3). Dimethylenecyclohexene **4** first undergoes a cycloaddition reaction

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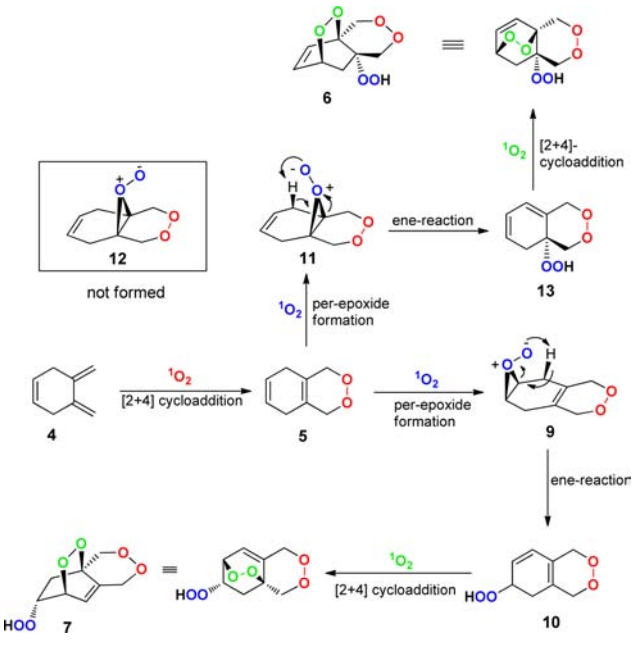
with singlet oxygen to give the dihydrodioxine derivative **5** with a cyclohexa-1,4-diene structure. The cyclohexa-1,4-diene unit in **5** undergoes an ene-reaction[12] with singlet oxygen. The two alkenes in **5** are inequivalent, and singlet oxygen can attack either one. When the singlet oxygen attacks the more substituted double bond, two diastereoisomeric perepoxides **11** and **12** may be formed. The product distribution shows the exclusive formation of the perepoxide **11**, where the pendent oxygen can abstract the allylic hydrogen from one of the methylene groups next to the double bond and form the hydroperoxide **13**. Probably, the repulsive interaction between the lone pairs of the oxygen atoms in the dioxine unit and the incoming oxygen molecule hinders the formation of **12**. Recently, we demonstrated that singlet oxygen attacks exclusively the more substituted double bond in 1,2-dimethylcyclohexa-1,4-diene.[13] However, in the case of **5**, the less substituted double bond was also attacked in a ratio of 1:6. If singlet oxygen attacks the sterically less crowded double bond in **5**, the perepoxide **9** can be formed, which would then rearrange to the hydroperoxide **10**.

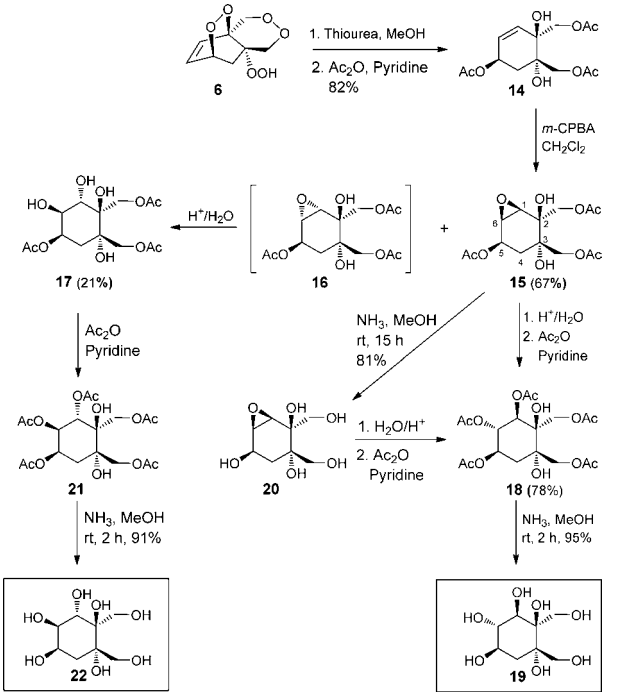
Scheme 3. Proposed Mechanism for the Formation of the Endoperoxides **6** and **7**



The stabilizing interaction of pendent oxygen with two allylic hydrogens on the same side of the double bond is responsible for the formation of *endo*-perepoxide **9**. This site selectivity of singlet oxygen was rationalized in terms of the electrophilic character of singlet oxygen.

In **5**, the reactivity of the more substituted double bond is decreased due to the inductive effect of oxygen atoms in dioxine rings. Hydroperoxides **10** and **13** with 1,3-diene faces have no plane of symmetry, and their 1,3-diene faces are inequivalent, so the third equivalent of singlet oxygen adds to the diene units from the less crowded face of the molecule to give **6** and **7**. To the best of our knowledge, this is the first reported reaction where 3 equiv of singlet oxygen are incorporated in a cascade process.[14]

Scheme 4. Synthesis of the Carbasugars **19** and **22**



The highly functionalized endoperoxides **6** and **7** are ideal substrates for the synthesis of carbasugars. For that reason the peroxide linkages in **6** were reduced by thiourea under very mild conditions, followed by acetylation of the primary and secondary hydroxyl groups to give **14** (Scheme 4). Since only oxygen−oxygen bonds break in this reaction, the configuration of all carbon atoms is preserved. The triacetate **14** was reacted with *m*-chloroperbenzoic acid to give a single epoxide **15** in 67% yield as well as the tetrol **17** (21%), which is probably formed by the ring-opening reaction of the initially formed *exo*-isomer **16**. The configuration of the epoxide **15** was determined by measuring the coupling constant between the acetoxy proton H_5 and epoxide proton H_6 ($J_{5,6}$ = 2.1 Hz) in $CDCl_3$.

The geometry optimized structure (DFT, B3LYP/6-31+G** level) of the epoxide **15** shows a dihedral angle of 54°, which is in agreement with the observed coupling

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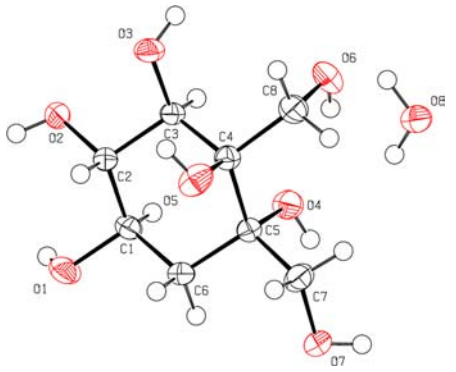

Figure 2. ORTEP diagram of **19**. Thermal ellipsoids are shown at the 50% probability level.

constant. The sulfuric acid catalyzed reaction of epoxy triacetate **15** in water followed by acetylation resulted in opening of the epoxide ring to afford pentaacetate **18**. Deacetylation of **18** with ammonia gave the hexol **19**, a new carbasugar, in 95% yield. The structure of **19** was confirmed by single crystal X-ray analysis (Figure 2). The molecule **19** crystallized from water in the monoclinic space group $P2_1/c$ with $Z = 4$. This configurational assignment shows that the epoxide ring in **15** underwent a *trans* ring-opening reaction without any anchimeric assistance. To prove this outcome, the acetate groups in **15** were removed with ammonia in methanol to give **20**. Acid catalyzed ring opening of **21** followed by acetylation afforded **18**, which was identical to the compound obtained by hydrolysis of **15**. With this chemical reaction, noninvolvement of the acetates in **15** in the ring-opening reaction was further proven. This may be attributed to the *cis*-configuration of the acetate group next to the epoxide ring in **15**.

The stereochemical course of the epoxidation of **14** may be *syn* or *anti* with respect to the adjacent acetoxy group.

We assumed that the second isomer, *anti*-isomer **16**, was also formed during the epoxidation reaction. Because of the *anti*-configuration of the neighboring acetate, this epoxide **16** may undergo a ring-opening reaction to afford **17**. The tetrol **17** was transformed into the corresponding pentatacetate for full characterization of the structure. Deacetylation of pentaacetate **21** with ammonia resulted in the formation of an isomeric hexol, **22**. The structure of **21** was confirmed by NMR spectral methods. Furthermore, a poor quality X-ray determination provided support for the structure.

In summary, with relatively little synthetic effort, we achieved the synthesis of two isomeric carbasugar derivatives, **19** and **22**, starting from 4,5-dimethylene-cyclohex-1-ene. The complex stereochemistry was introduced in a single step, by means of a photooxygenation reaction. To the best of our knowledge, this is the first case in which singlet oxygen undergoes three cascade reactions. Cleavage of the peroxide linkages in **6** followed by oxidation of the double bond and ring-opening reaction resulted in the formation of two new carbasugars. Further applications of singlet oxygen to the synthesis of carbasugars with complex structures are currently in progress.

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Supporting Information Available. Experimental conditions, spectroscopic data (1D and 2D NMR spectra), crystallographic information (CIF) of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.