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Tetrahedron: *Asymmetry* 17 (2006) 1780–1785

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Synthesis and spectroscopic NMR studies of a highly stable cross-ozonide product derived from a carbohydrate system

María I. Mangione,[a] Sebastián A. Testero,[a] Alejandra G. Suárez,[a]
Rolando A. Spanevello[a,*] and Jean-Pierre Tuchagues[b]

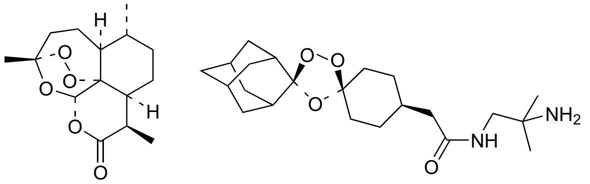
[a] *Instituto de Química Orgánica de Síntesis, Facultad de Ciencias Bioquímicas y Farmacéuticas—Universidad Nacional de Rosario-CONICET, Suipacha 531, S2002LRK Rosario, Argentina*
[b] *Laboratoire de Chimie de Coordination du CNRS, UPR 8241, 205 Route de Narbonne, 31077 Toulouse Cedex, France*

Received 10 April 2006; accepted 5 June 2006
Available online 18 July 2006

Abstract—Ozonolysis of a carbohydrate derived norbornene system afforded a stable intramolecular cross-ozonide through a stereocontrolled pathway involving a regioselective fragmentation of the primary ozonide.

1. Introduction

The chemistry of endoperoxides and trioxolane systems has gained much popularity over the last decade because they were recognized as structures widely distributed in nature, mostly due to their inherent biological properties.[1] A great deal of effort has been directed towards studying the chemistry and biological mode of action of artemisinin **1** (Fig. 1) and a plethora of analogues. Artemisinin[2] is a natural product from a traditional Chinese herbal remedy and has shown a potent antimalarial activity.[3] The fact that this type of compound has been used as a model for the design of new therapeutic agents against resistant forms of *Plasmodium falciparum* led to the development of simpler cyclic peroxide structures with important antimalarial activity.[4]



1: Artemisinin **2: OZ 277**

Figure 1.

More recently, a new drug candidate named OZ 277 **2** has strongly emerged as a new antimalarial agent.[5] The unique structural similarity that this synthetic ozonide exhibits with artemisinin is the peroxide bridge, which is critical for the pharmacological activity.

The synthesis of 1,2,4-trioxolane rings is usually achieved through ozonolysis of a carbon–carbon double bond. The mechanism of the ozonolysis reaction proposed by Criegee consists of three steps: (i) a [3+2] cycloaddition reaction of ozone with the alkene leading to the formation of a primary ozonide or 1,2,3-trioxolane **3**, (ii) a cycloreversion process providing the transient carbonyl oxide and a stable carbonyl compound, which may proceed in two different ways in the case of unsymmetrically substituted alkenes **4a** and **4b**, (iii) recombination of the carbonyl oxide and the newly formed carbonyl group derivative to give 1,2,4-trioxolane **5**.[6] In the case where the transient carbonyl oxide is trapped by another carbonyl derivative present in the reaction medium, the product is a cross-ozonide **6a** and **6b**[7] (see Scheme 1).

Alternatively, when the ozonolysis reaction is performed in a participating solvent, such as an alcohol, the carbonyl oxide can react with the solvent to give an alkoxy hydroperoxide, which upon the appropriate workup yields the corresponding ester.[8] In the last two cases, the reaction products provide useful information regarding the regioselectivity of the primary ozonide cleavage.[9]

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* Corresponding author. Tel./fax: +54 341 4370477; e-mail: rspaneve@fbioyf.unr.edu.ar

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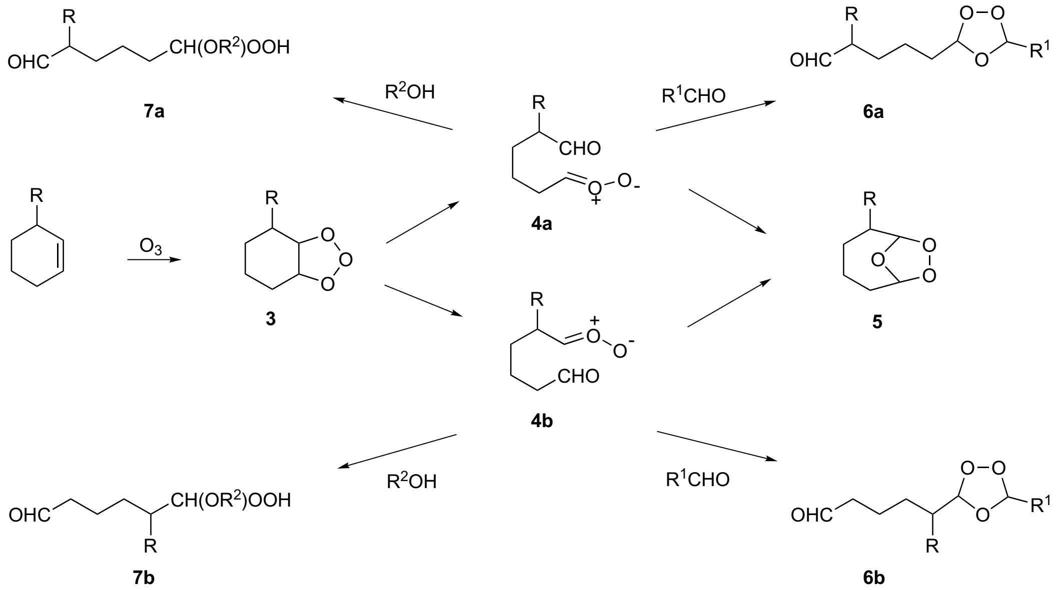
doi:10.1016/j.tetasy.2006.06.006



Scheme 1.

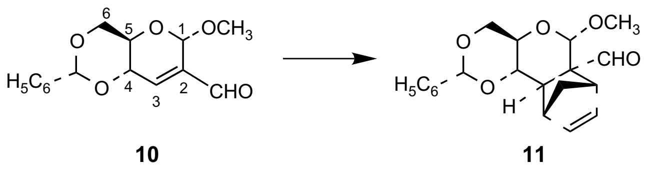
2. Results and discussion

In this context, we report the synthesis of an enantiomerically pure and highly stable intramolecular cross-ozonide structure. The product was obtained by means of a non-symmetric ozonolysis of a norbornene type skeleton derived from a carbohydrate system.

Our enantiospecific route relies on the use of D-glucose as source of chirality and employed the pyranoside ring as the initial scaffolding for constructing a dienophile with an exocyclic electron withdrawing group. In a simple and efficient synthetic sequence, methyl-α-D-glucopyranoside **8** was converted into a cyclic α,β-unsaturated aldehyde **10** (Scheme 2).[10]

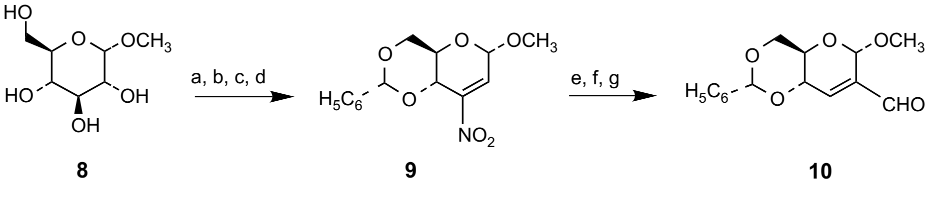
The reaction of aldehyde **10** with freshly cracked cyclopentadiene afforded the cycloadduct **11** in 26% yield as the major adduct (Scheme 3). The product was the result of the diene approach from the β face of dienophile **10** in an *endo* manner. We were surprised with the outcome and low yield of this reaction, since the isomeric dienophile (with the carbonyl group attached at C-3) afforded the corresponding β-*exo* adduct in 85% yield as a single product under similar reaction conditions.[11,12]

The structure assignment of **11** was based on spectroscopic evidence. All its ^{1}H and ^{13}C NMR signals were unequivocally assigned by using homo and heteronuclear 2D NMR techniques and NOE experiments.



Scheme 3. Reagents and conditions: $LiClO_4$ anhydrous 5 M in Et_2O, cyclopentadiene, rt.

The proton spectrum showed four sharp singlets at 3.42, 4.84, 5.51, and 9.53 ppm that were assigned as the methoxy group, the anomeric proton H-3, the benzylic proton H-8, and the aldehyde proton, respectively. Two broad singlets at 2.96 and 3.14 ppm correspond to the bridge head protons H-1 and H-12. A well defined double doublet at 4.33 ppm was attributed to the equatorial H-6 and two other double doublets centered at 6.08 and 6.19 ppm were assigned to the vinylic protons H-13 and H-14. Another characteristic multiplet that integrated for two protons appeared at 1.63 ppm and was attributed to the methylene group C-15. A coupling constant of 9.18 Hz between the vicinal protons H-10 and H-11 clearly showed a *trans* relationship, suggesting that the product was formed by the approach of the cyclopentadiene from the β face of the



Scheme 2. Reagents and conditions: (a) $NaIO_4$, H_2O, pH 5–6; (b) CH_3NO_2, $NaOCH_3$, CH_3OH; (c) $C_6H_5CH(OCH_3)_2$, CSA, $CHCl_3$; (d) MsCl, Et_3N, CH_2Cl_2; (e) KCN, H_2O, Amberlite, CH_3CN; (f) Et_3N, acetone/H_2O; (g) DiBAL-H, CH_2Cl_2.