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Recent Progress in the Synthesis of Promising bicyclo[4.3.1]decanes by the Oxidative Rearrangement Reaction of bicyclo[4.2.2]decatetraenes †

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Abstract: Data on the synthesis of practically important bicyclo[4.3.1]decatrienes based on oxidative transformations of bicyclo[4.2.2]deca-2,4,7,9-tetraenes are summarized. The authors have shown for the first time that the reactions of electrophilic activation of double bonds in bicyclo[4.2.2]deca-2,4,7,9-tetraenes under the action of *m*-chloroperbenzoic acid are accompanied by oxidative skeletal rearrangement with the formation of bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols. A probable mechanism for the detected rearrangement is proposed. Data on the study of the antitumor properties of the resulting bicyclo[4.3.1]decatrienes are presented, among which samples with high antitumor activity were identified.

Keywords: 1,3,5,7-cyclooctatetraene; [6+2]-cycloaddition; bicyclo[4.2.2]deca-2,4,7,9-tetraene; oxidative rearrangement; bicyclo[4.3.1]deca-2,4,8-triene-7,10-diol; antitumor activity

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1. Introduction

The bicyclo[4.3.1]decane core is the key structural unit of many natural biologically active compounds, for example, caryolane, phomoidride B, vibsanines, welwitindolinones, nakafuran-9, pallescensins C and D, florlides and so on [1–4], which exhibit anti-HIV, antitumor, antimicrobial, antibacterial, and antimicotic properties.

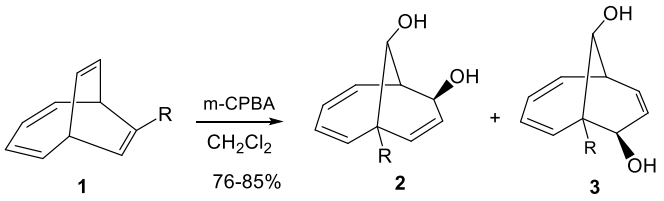
The most popular methods for the formation of bicyclo[4.3.1]decanes are based on metathesis, intramolecular Diels-Alder reaction, Pd-catalyzed [6+3]-cycloaddition of trimethylenemethane to tropones, and Cu-catalyzed [3+3]-cycloaddition of propargyl esters to cyclic enamines [1,5–7]. There is also a single example of the synthesis of bicyclo[4.3.1]deca-2,4,8-trienes via electrophilic activation of the double bonds of bicyclo[4.2.2]deca-2,4,7,9-tetraene by bromination or hydrobromination [8].

The electrophilic activation reaction of bicyclo[4.2.2]deca-2,4,7,9-tetraenes has a great synthetic potential, as it leads to the formation of bicyclo[4.3.1]decanes containing reactive functional groups in the structure, which opens up prospects for further directed transformations into useful substances with desired properties.

2. Results and Discussion

In 2017, we first reported an efficient method for the synthesis of previously undescribed bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols based on the electrophilic addition of *m*-chloroperbenzoic acid to bicyclo[4.2.2]deca-2,4,7,9-tetraenes [9]. As a result of the interaction of substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes 1 [9–13] with

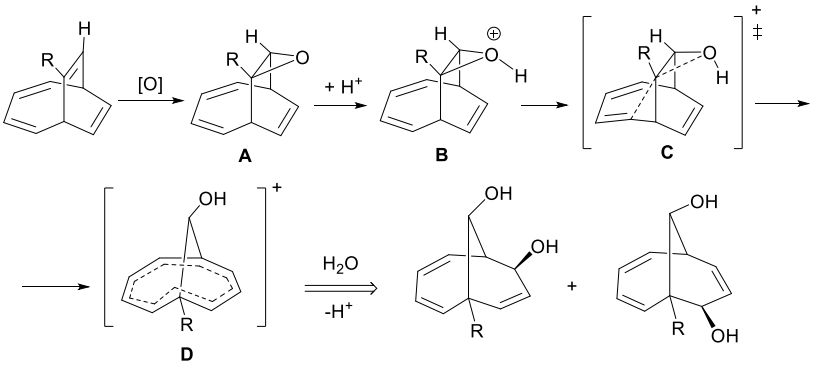
m-chloroperbenzoic acid, taken in a ratio of 1:1.4 (CH_2Cl_2, 0 °C (3 h), 25 °C (12 h)), the target bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols are formed as two regioisomers 2 and 3 [9,10] (Scheme 1). Both regioisomers have *anti*- and *exo*-orientation of hydroxyl groups.



R = Ar, Alk, $CH(CH_2)n$, $-(CH_2)_4-CCSiMe_3$, n = 2, 4, 5

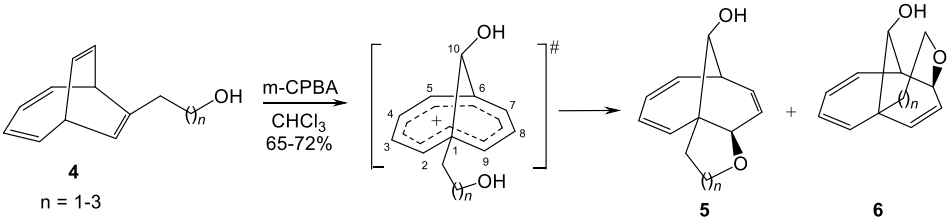
Scheme 1. Reaction of bicyclo[4.2.2]deca-2,4,7,9-tetraenes with *m*-chloroperbenzoic acid.

Presumably, the formation of bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols includes the following steps [9]. Initially, one of the carbon-carbon double bonds of bicyclo[4.2.2]deca-2,4,7,9-tetraene is oxidized to form epoxide **A**. Further protonation of the epoxide oxygen atom leads to cation **B**, which undergoes intramolecular rearrangement. The transformation of intermediate **B** into **D** proceeds almost barrier-free through the butterfly-shaped transition state **C**. Intermediate **D** is a substituted bis-homotropylium cation having a homoaromatic character [14]. At the final stage, hydrolysis of the intermediate bis-homotropylium cation **D** occurs [9] (Scheme 2).



Scheme 2. Putative mechanism for the transformation of substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes into substituted bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols under the action of *m*-chloroperbenzoic acid.

Fairly interesting results were obtained upon the oxidation of 7-(ω-hydroxyalkyl)bicyclo[4.2.2]deca-2,4,7,9-tetraenes 4. The reaction of bicyclo[4.2.2]deca-2,4,7,9-tetraenes 4 with *m*-chloroperbenzoic acid is accompanied by intramolecular cyclization to give tricyclic alcohols 5 and 6 [9] (Scheme 3).

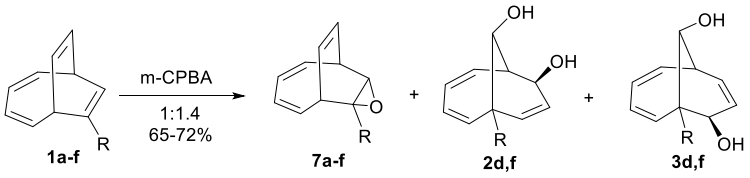


Scheme 3. Reaction of 7-(ω-hydroxyalkyl)bicyclo-[4.2.2]deca-2,4,7,9-tetraenes with *m*-chloroperbenzoic acid.

This reaction is a result of the fact that cation (Scheme 3) contains a hydroxyl group that can act as a nucleophile. As noted above, the reaction gives rise to a bis-homotropylium cation. Thus, the hydroxyl attacks the electrophilic site of the bis-homotropylium cation; this furnishes a five-, six-, or seven-membered ring.

In view of the relevance of the above-indicated studies and in order to extend the scope and identify new trends of the discovered oxidative skeletal isomerization of bicyclo[4.2.2]deca-2,4,7,9-tetraenes induced by *m*-chloroperbenzoic acid, we set ourselves the task to study, for the first time, the oxidation of bicyclo[4.2.2]deca-2,4,7,9-tetraenes containing chemically different functional groups: phthalimide, nitrile, and ester groups [15]. We found that the oxidation of nitrile-substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes [11,12] **1a,b** with *m*-chloroperbenzoic acid taken in stoichiometric amounts under the previously developed conditions [9] ($CHCl_3$, 0 °C (3 h) → 40 °C (3 h) → 25 °C (12 h)) results in the formation of only epoxides, namely, substituted 8-oxatricyclo[4.3.2.$0^{7,9}$]undeca-2,4,10-trienes **7a,b.** The respective diols are not formed in these reactions (Scheme 4). Presumably, the epoxy group in the initially formed epoxy carbocycles **7a,b** is stabilized by donor-acceptor interaction with the nitrile group and does not undergo protonation that would lead to skeletal isomerization [15].

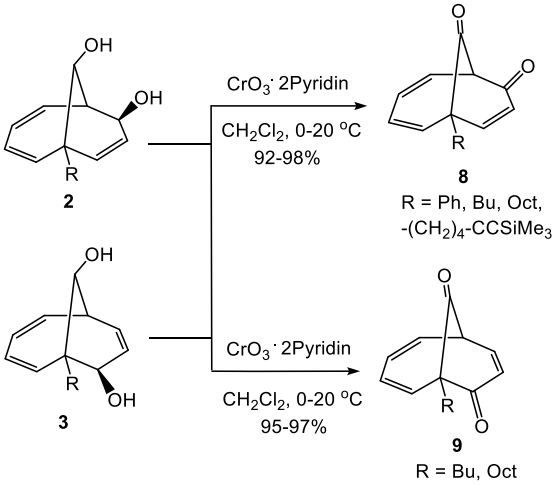
Conversely, the nature of products formed in the reaction of substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes [11,12] **1c,d** containing a phthalimide group depends on the linker alkyl chain length. In the case of bicyclo[4.2.2]deca-2,4,7,9-tetraene **1c** with the phthalimide substituent separated from the bicyclic core by two methylene group, only epoxide **7c** is formed. Meanwhile, the reaction with bicyclo[4.2.2]deca-2,4,7,9-tetraene **1d** containing a phthalimide group separated from the core by four methylene units gives epoxide **7d** together with bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols **2d** and **3d** in 1/1/1 ratio. Similar results were obtained in the reaction of bicyclo[4.2.2]deca-2,4,7,9-tetraenes **1e,f** containing the methoxycarbonyl group [15] (Scheme 4).



	7/2/3
a: R = $(CH_2)_2CN$	1/0/0
b: R = $(CH_2)_3CN$	1/0/0
c: R = 2-phthalimidoethyl	1/0/0
d: R = 2-phthalimidobutyl	1/1/1
e: R = $(CH_2)_2COOMe$	1/0/0
f: R = $(CH_2)_3COOMe$	1/1/1

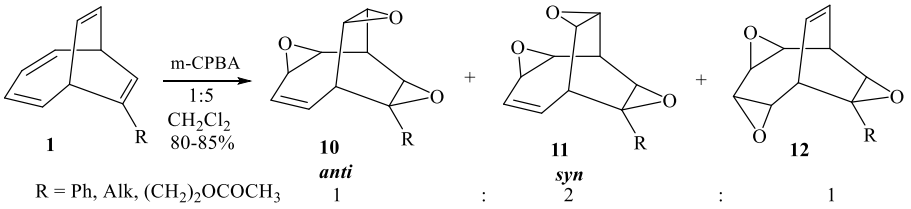
Scheme 4. Reaction of bicyclo[4.2.2]deca-2,4,7,9-tetraenes with *m*-chloroperbenzoic acid.

It is necessary to mention that the hydroxyl groups present in the bicyclo[4.3.1]deca-2,4,8-triene-7,10-diol molecule are by themselves reaction sites bearing a huge potential for further transformations. For example, oxidation of the hydroxyl groups of bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols **2** and **3** on treatment with Sarett reagent, a chromium oxide complex with pyridine, furnished bicyclo[4.3.1]deca-2,4,8-triene-7,10-diones **8** and **9** in virtually quantitative yields [9] (Scheme 5).



Scheme 5. Sarett oxidation of bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols.

Having obtained nontrivial results in the oxidation of substituted bicyclodecatetraenes with *m*-chloroperbenzoic acid, we studied the reactions of oxidation of these cycloadducts with an excess of *m*-chloroperbenzoic acid. It was found that the oxidation of alkyl(phenyl)-substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes 1 with *m*-chloroperbenzoic acid taken in 1:5 ratio affords pentacyclic epoxides 10-12 (1:2:1 ratio) [16] (Scheme 6).



Scheme 6. Oxidation of substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes with *m*-chloroperbenzoic acid.

Considering the structural similarity of the prepared bicyclo[4.3.1]decanes with some natural compounds [1], which exhibit a wide range of biological activities, it seemed of practical interest to assess the antitumor activity *in vitro* of some of the compounds that were synthesized. We have found that synthesized bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols possessed high antitumor activity *in vitro* against tumor cell lines Hek293, Jurkat, K562, A549 and HL-60 [9,10,15].

3. Conclusions

Thus, we have for the first time carried out the oxidation of bicyclo[4.2.2]deca-2,4,7,9-tetraenes with m-chloroperbenzoic acid to form bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols with high yields (65–85%). The proposed method for the synthesis of the bicyclo[4.3.1]decane system may serve as an alternative to the existing methods for preparation of molecules of this type and could be used at the key steps of the syntheses of important biologically active compounds.

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