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Oxidative skeletal rearrangement of bicyclo[4.2.2]deca-2,4,7,9-tetraenes to bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols and study of the antitumor activity of the products *in vitro*

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ABSTRACT

Bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols were synthesized in 76–85% yields by oxidative skeletal isomerization of the substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes of various structures on treatment with *m*-chloroperbenzoic acid. The structures of the obtained bicyclic unsaturated diols were reliably proven by modern spectral methods and X-ray diffraction. A high antitumor activity *in vitro* was found for bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols against the Jurkat, K562, U937 and HL-60 tumor cell lines.

According to published data [1], the bicyclo[4.3.1]decane cage is a widely encountered structural unit present in a large number of natural compounds (caryolanes, phomoidride B, vibsanins, welwitindolinones, nakafuran-9, pallescensins C and D, and florlide classes), which exhibit a broad spectrum of biological activities [2].

The methods for the synthesis of bicyclo[4.3.1]decanes known from the literature are based on the use of reactions such as intramolecular Diels-Alder cyclization of polyenes, olefin metathesis, Pd-catalyzed [6π+3π]-cycloaddition of trimethylenemethane to tropones, [3π+3π]-cycloaddition of propargyl esters to cyclic enamines catalyzed by Cu complexes, and electrophilic addition of Br_2, HBr, $Hg(OAc)_2$, and chlorosulfonyl isocyanate to bicyclo[4.2.2]deca-2,4,7,9-tetraenes (BDTs) [1a,3]. BDTs are accessible compounds owing to the lately developed Co-catalyzed [6 + 2]-cycloaddition reactions of alkynes with 1,3,5,7-cyclooctatetraene (COT) [4].

Recently [4b], using a moderate number of simple alkyl- and phenyl-substituted BDTs, we have demonstrated the possibility of easy skeletal oxidative isomerization of the above BDTs via the reaction with *m*-chloroperbenzoic acid to give substituted bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols (Scheme 1).

As noted by the authors [4b], the reaction of 7-phenylbicyclo[4.2.2]deca-2,4,7,9-tetraene with *m*-chloroperbenzoic acid under the chosen conditions gives only one regioisomer, 1-phenylbicyclo[4.3.1]deca-2,4,8-triene-7,10-diol **A**, while the reactions of 7-alkylbicyclo[4.2.2]deca-2,4,7,9-tetraenes afford two regioisomers **B** and **C** in equal amounts (Scheme 1).

In addition, it has been found [4b] that diols **A-C** and their keto derivatives possess high antitumor activity against the Hek293, Jurkat, K562, and A549 cell lines.

In view of the mentioned tentative results [4b] and in order to extend the scope of applicability of the discovered oxidative skeletal isomerization of BDTs to bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols, here we set ourselves the tasks, first, to study the effect of the structure of the starting alkynes on the pathway and selectivity of their catalytic [6π+2π]-cyclocodimerization with COT and, second, to perform the oxidative skeletal isomerization of the obtained BDTs to bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols with *m*-chloroperbenzoic acid. In order to search for and develop modern antitumor agents, we also planned to study the antitumor activities of the resulting bicyclic diols.

As the initial compounds for implementing this plan, we chose

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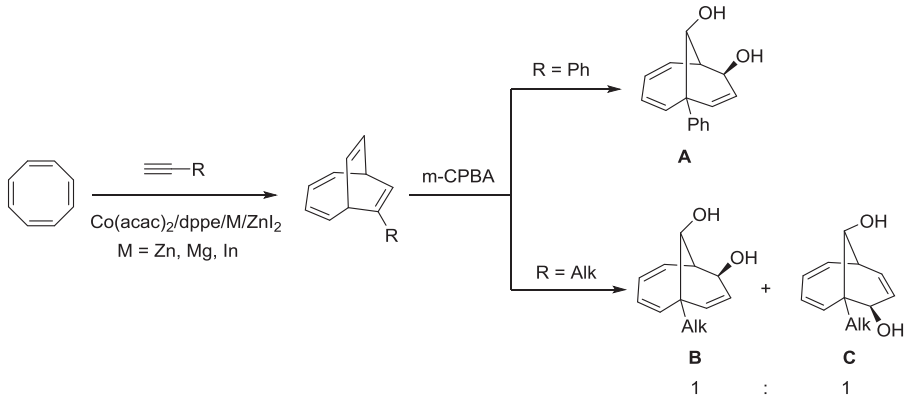


Scheme 1. Reaction of alkyl- and phenyl-substituted BDTs with *m*-CPBA.

terminal acetylenes containing *meta- and para*-tolyl, *para*-methoxyphenyl, bromo(chloro, fluoro)phenyl, naphthyl, phenanthrenyl, and cycloalkyl substituents **1a-j** and employed them to prepare BDTs in the presence of the $Co(acac)_2$/dppe/Zn/ZnI_2 catalytic system proposed in our previous study [4b].

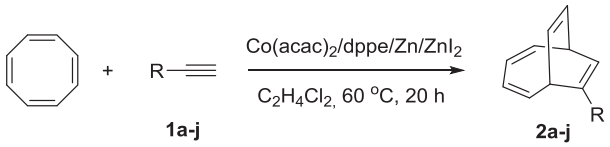
Under the selected optimal conditions (alkyne:COT:$Co(acac)_2$:dppe:Zn:ZnI_2 = 1:1.2:0.1:0.1:0.3:0.2, $C_2H_4Cl_2$, 20 h, 60 °C), the [6π+2π]-cyclocodimerization of COT with the above-listed terminal alkynes **1a-j** gives substituted BDTs **2a-j** in 76–88% yields (Scheme 2).

The structures of the obtained BDTs were proved by modern IR and NMR spectroscopy and mass spectrometry techniques.

The next stage of our research comprised the oxidative skeletal isomerization of the synthesized BDTs on treatment with *m*-chlorobenzoic acid under the developed conditions ($CHCl_3$, 0 °C (3 h), 40 °C (3 h), 25 °C (12 h)). These experiments showed that aryl-substituted BDTs **2a-e** are converted to substituted bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols **4a-e** with high regio- and stereoselectivity. The oxidation of cycloalkyl-substituted BDTs **2f-h** with *m*-chlorobenzoic acid under the selected conditions affords regioisomeric bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols **4f-h** and **5f-h** in 3:1 ratio, respectively (Scheme 3).

As regards naphthyl- and phenanthrenyl-substituted BDTs **2i,j**, these tetraenes do not undergo the oxidative skeletal isomerization. Apparently, the presence of bulky aromatic electron-withdrawing groups at the substituted double bond of BDTs not only decreases the reactivity of this bond towards the electrophilic peracid, but also sterically hampers the reagent approach, and, as a result, precludes the epoxidation.

The oxidation of substituted BDTs under the action of *m*-chlorobenzoic acid is accompanied by rearrangement of the carbon cage of the molecule and presumably involves the formation of intermediates **3a-j**, which represent substituted bis-homotropylium



a: R = 4-$CH_3C_6H_4$ (80%)
b: R = 3-$CH_3C_6H_4$ (82%)
c: R = 4-BrC_6H_4 (79%)
d: R = 3-ClC_6H_4 (78%)
e: R = 4-FC_6H_4 (76%)
f: R = $CH(CH_2)_2$ (85%)
g: R = $CH(CH_2)_4$ (88%)
h: R = $CH(CH_2)_5$ (80%)
i: R = 1-naphthyl (78%)
j: R = 9-phenanthrenyl (76%)

Scheme 2. Cobalt-catalyzed [6 + 2]-cycloaddition of COT with alkynes **1a-j**.

cations [4b]. The bulky phenyl group at C(1) in BDTs **2a-e** decreases the steric accessibility of the electrophilic carbon atom; therefore, the reaction involves only C(7) and gives only one regioisomer **4a-e**. In the case of cycloalkyl-substituted bis-homotropylium cation, the steric factor is less significant and, therefore, the nucleophilic attack is directed not only at C(7), but also at C(9) to give two regioisomers **4f-h** and **5f-h**.

The product structures were reliably proved by 1D and 2D NMR techniques and X-ray diffraction analysis. Among the bicyclic diols we obtained, *p*-fluorophenyl-substituted bicyclo[4.3.1]deca-2,4,8-triene-7,10-diol **4e**, is crystalline; we were able to grow crystals of compound **4e** and performed an X-ray diffraction study, which unambiguously proved that the hydroxyl group at the bridging carbon atom has *anti*-orientation relative to the butadiene skeleton and the hydroxyl group at C_7 has *exo*-orientation relative to the bridging moiety (Fig. 1).

For bicyclo[4.3.1]deca-2,4,8-triene-7,10-diol **5h** (Fig. 2), X-ray diffraction data also prove the *anti*-orientation of the hydroxyl group at the bridging carbon atom and the *exo*-orientation of the hydroxyl group at C(7). According to 2D NMR experiment, the second regioisomer **4h** is also characterized by the *anti*- and *exo*-orientations of the hydroxyl groups.

1. The antitumor activity *in vitro* of bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols

Previously [4b], we have found that 1-phenylbicyclo[4.3.1]deca-2,4,8-triene-7,10-diol possessed high antitumor activity *in vitro* against tumor cell lines Hek293, Jurkat, K562 and A549 (IC50 of 0.84 ± 0.09 to 1.74 ± 0.18 μM), and the cytotoxic activity of 1-butylbicyclo[4.3.1]deca-2,4,8-triene-7,10-diol varied across these cell lines within the range of 1.12 ± 0.11–2.1 ± 0.2 μM.

In continuation of this research, and also in order to study the effect of the structure and nature of the substituent in the synthesized bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols upon their antitumor activity, we have tested *in vitro* the compounds **4a-h** and **5f-h** on the tumor cell lines Jurkat, K562, HL-60, and U937.

It was established that bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols **4a** and **4b** containing *p*- and *m*-tolyl substituents exhibited practically the same cytotoxic activity on all cell lines used (Table 1).

The introduction of halogen (**4c-e**) into the aromatic fragment led to a significant increase in the cytotoxicity of the bicyclic compounds under study in the *m*-Cl (**4d**) < *p*-Br (**4c**) < *p*-F (**4e**) series.

The study of the antitumor activity of isomeric bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols **4f-h** and **5f-h** has shown that, in each pair of compounds, isomers **5f-h** were the most active. In this case,