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Reactions of functionally substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes with *m*-chloroperbenzoic acid and *in vitro* evaluation of product cytotoxicity against tumor cells

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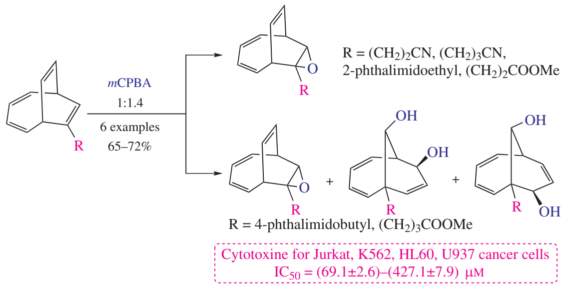
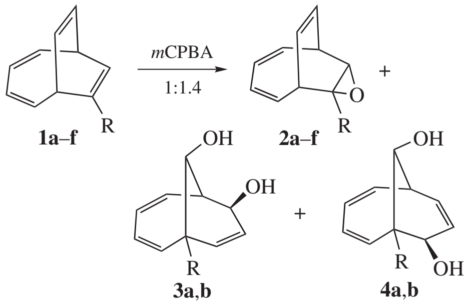
The oxidation of functionally substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes with *m*-chloroperbenzoic acid affords practically valuable 8-oxatricyclo[4.3.2.0^{7,9}]undeca-2,4,10-trienes and bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols in yields of 65–72%. The structures of the products were established by advanced spectral methods and X-ray diffraction analysis. The new compounds were screened for *in vitro* cytotoxicity against Jurkat, K562, U937 and HL60 tumor cell lines.



Bicyclo[4.2.2]deca-2,4,7,9-tetraenes (BDTs) undergo skeletal rearrangements under the action of electrophilic reagents with the formation of bicyclo[4.3.1]deca-2,4,7-trienes.[1] Recently, we found[2] that oxidation of 7-alkyl-, aryl-, cycloalkyl-, and hydroxyalkyl-substituted BDTs with *m*-chloroperbenzoic acid (*m*CPBA) is accompanied by skeletal isomerization to bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols. In experiments involving 7-hydroxyalkyl-bicyclo[4.2.2]deca-2,4,7,9-tetraenes, intramolecular heterocyclization occurred together with skeletal isomerization to afford tricyclic alcohols. The obtained results indicate that the skeletal isomerization pathway and the structure of resulting bicyclic diols are markedly dependent on the nature of the substituent in the starting BDT. The prepared bicyclic diols and their keto derivatives possess high antitumor activities against the Hek293, Jurkat, K562, A549, Hek293, U937 and HL-60 tumor cell lines.[2] It is noteworthy that the interest in this family of functionally substituted bicyclo[4.3.1]decanes grows also because the bicyclodecane cage is the key structural unit of a number of natural bioactive compounds (caryolane, phomoidride B, vibsanines, welwitindolinones, nakafuran-9, pallescensins C and D, florlides).[3,4]



	2 / 3 / 4	Yield (%)
a R = 4-phthalimidobutyl	1 : 1 : 1	69
b R = (CH$_2$)$_3$COOMe	1 : 1 : 1	65
c R = (CH$_2$)$_2$CN	1 : 0 : 0	72
d R = (CH$_2$)$_3$CN	1 : 0 : 0	68
e R = 2-phthalimidoethyl	1 : 0 : 0	71
f R = (CH$_2$)$_2$COOMe	1 : 0 : 0	67

Scheme 1

Thus, in view of the relevance of the above data and in order to extend the scope of analogous valuable compounds, we herein studied the *m*CPBA oxidation of some other BDTs bearing different functional groups such as phthalimide, nitrile and ester ones (Scheme 1).

We found that the oxidation of nitrile-substituted BDTs[5,6] **1c**,**d** with stoichiometric amounts of *m*CPBA under the previously developed conditions[2] [CHCl$_3$, 0 °C (3 h) → 40 °C (3 h) → 25 °C (12 h)] affords only epoxides, namely, substituted 8-oxatricyclo[4.3.2.0^{7,9}]undeca-2,4,10-trienes **2c**,**d**. The respective diols of type **3**,**4** (see Scheme 1) are not formed. Presumably, the epoxy group in the initially formed epoxy carbocycles **2c**,**d** is stabilized by donor–acceptor interaction with the nitrile group and does not undergo protonation that could cause skeletal isomerization.

Conversely, the nature of products formed in the reaction of phthalimide-equipped BDTs[5,6] **1a**,**e** depends on the linker alkyl chain length. In the case of BDT **1e** with 2-phthalimidoethyl substituent, only epoxide **2e** is formed. Meanwhile, the reaction with BDT **1a** containing 4-phthalimidobutyl group gives epoxide **2a** together with bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols **3a** and **4a** in 1 : 1 : 1 ratio. The products were separated by column chromatography. Similar results were obtained in the reaction of BDTs **1b**,**f** containing the methoxycarbonyl group (see Scheme 1).

The structures of products **2–4** were reliably proved by 1D and 2D NMR spectroscopy techniques[†] and X-ray diffraction analysis of crystalline epoxide **2c** (Figure 1).[‡]

[†] For procedures and characteristics of the products, see Online Supplementary Materials.

[‡] *Crystallographic data for* **2c**. Crystals of C$_{13}$H$_{13}$NO (M = 199.24) are orthorhombic, space group $Pbca$, at 293 K: a = 7.8596(11), b = 14.0911(14) and c = 19.2901(19) Å, β = 90°, V = 2136.4(4) Å^3, Z = 8, d_{calc} = = 1.239 g cm^{-3}, μ(MoKα) = 0.079 mm^{-1}, F(000) = 848.0 reflections were

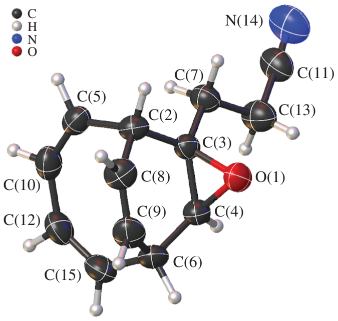
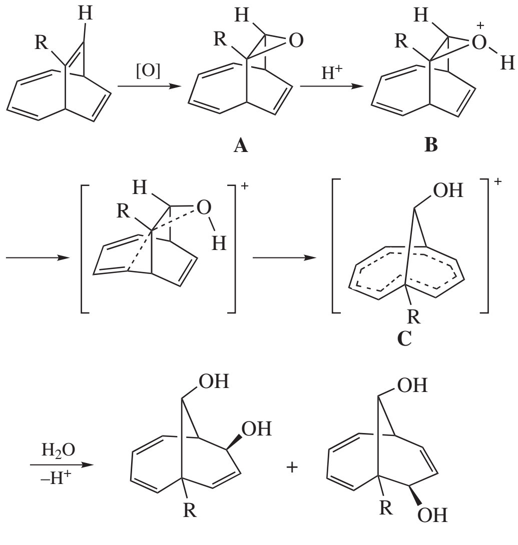


Figure 1 Structure of compound **2c** in the crystal (ellipsoid contour probability 50%).

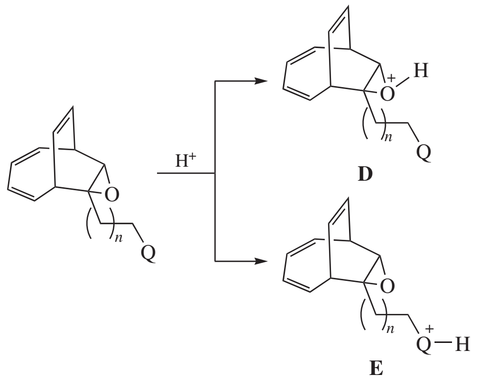
Most likely,[2(*a*)] the formation of diols **3**,**4** includes the following stages: (1) oxidation of one carbon–carbon double bonds of BDT to give epoxide **A**; (2) subsequent protonation of the epoxide oxygen to give cation **B**; (3) intramolecular rearrangement of cation **B**; (4) hydrolysis of the intermediate bis-homotropylium cation **C** (Scheme 2).

Thus, unlike phenyl- or alkyl-substituted BDTs,[2(*a*)] compounds **1c**–**f** react with *m*CPBA to give only epoxides. In the case of compounds **1a**,**b**, diols are formed together with epoxides.

In order to substantiate the obtained results and elucidate the factors affecting the nature of the products of oxidation of BDTs **1a**–**f**, we carried out quantum chemical modeling of the intramolecular rearrangement of cation **B**. From analysis of the electronic effects of substituents in the BDT molecule, it is obvious that epoxide ability to undergo the rearrangement decreases with increasing –I effect of the substituent at the double bond. However, the B3LYP/6-31G(d,p) calculation results indicate that the difference between the activation energies for the intramolecular rearrangement of cations formed upon epoxide protonation is insignificant for all of the considered compounds and varies from –0.38 to 10.71 kJ mol^{-1}, which is obviously insufficient to account for the experimentally observed substantial difference between the compound reactivities. We assumed that the presence of two nucleophilic centers in the epoxide molecule may considerably affect the chemical behavior of BDTs towards this reaction. Indeed, it can be assumed that the substituent functional group in epoxides **2c**–**f** can be protonated during the reaction, which would hamper protonation of the epoxide oxygen atom needed for the rearrangement to occur (Scheme 3).



Scheme 2



Scheme 3

The changes in the Gibbs free energy upon protonation of the functional group and the epoxide oxygen atom calculated by B3LYP/6-31G(d,p) are summarized in Table 1. Compounds, which give only epoxides in the reaction, are characterized by smaller differences between the Gibbs free energies of formation of cations *via* protonation of the functional group and the epoxide group. It follows from Table 1 that epoxide protonation is the prevailing pathway of the gas phase reaction. However, when solvation is taken into account, the situation can crucially change, because interaction of the charged group present in the side chain with solvent molecules should be more efficient than the solvation of the sterically hindered protonated epoxide.

It is known that alkyl-, aryl- and hydroxy-substituted derivatives of bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols exhibit moderate citotoxicity against a number of tumor cell lines.[2] Therefore, it seemed interesting to study the influence of the nature of the substituent and the structure of the newly synthesized epoxides **2a**–**f** and diols **3a**,**b** and **4a**,**b** on their *in vitro* cytotoxic activity against Jurkat, K562, U937 and HL60 tumor cell lines (Table 2).

Epoxy compounds **2a**,**b**,**f** containing phthalimide or ester groups have exhibited the greatest cytotoxic activity. An increase in the number of the methylene units between the functional group and bicyclic or tricyclic fragment induces an increase in the cytotoxicity

Table 1 Changes in the Gibbs free energy upon protonation of the functional group and the epoxide oxygen atom calculated by B3LYP/6-31G(d,p).

$(CH_2)_nCH_2Q$	$\Delta G^0_{f,\,298}$ (**D**)/ Hartrees	$\Delta G^0_{f,\,298}$ (**E**)/ Hartrees	$\Delta G^0_{f,\,298}$ (**D**)– –$\Delta G^0_{f,\,298}$ (**E**)/ kJ mol^{-1}
CH_2CH_2OH	–616.199282	–616.169438	–78.37
$CH_2CH_2CH_2COOMe$	–808.123802	–808.102135	–56.90
$CH_2CH_2CH_2CN$	–672.516964	–672.500439	–43.39
CH_2CH_2COOMe	–768.832948	–768.819375	–35.65
CH_2CH_2CN	–633.222376	–633.213045	–24.52

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measured and 2523 independent reflections (R_{int} = 0.0240) were used in a further refinement. The refinement converged to wR_2 = 0.1436 and GOF = 1.021 for all independent reflections [R_1 = 0.0554 was calculated against F for 3458 observed reflections with $I > 2\sigma(I)$]. X-ray diffraction analysis was performed on an XCaliburEos four-circle automated diffractometer (graphite monochromator, MoKα radiation, λ = 0.71073 Å, ω-scan mode, $2\theta_{\max}$ = 62°). The data were collected and treated using the CrysAlis$^{\text{Pro}}$ (Oxford Diffraction Ltd.) program package, version 1.171.36.20. The structures were solved by the direct method and refined by the full-matrix least-squares method in the anisotropic approximation for non-hydrogen atoms. The hydrogen atoms were located on electron density maps and refined in the isotropic approximation. The refinement was done using SHELX97 program package.[7]

CCDC 1887623 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

Table 2 *In vitro* cytotoxic activities of synthesized 8-oxatricyclo[4.3.2.$0^{7,9}$]undeca-2,4,10-trienes **2a**–**f** and bicyclo[4.3.1]deca-2,4,8-triene-7,10-diols **3a**,**b** and **4a**,**b** measured on tumor cell cultures (Jurkat, K562, HL60, U937).

Compound	Cytotoxic activity/μmol dm^{-3}			
	Jurkat	K562	U937	HL60
2a	74.1 ± 2.7	83.5 ± 3.1	73.1 ± 2.4	69.1 ± 2.6
2b	88.2 ± 2.5	98.1 ± 3.7	84.4 ± 3.1	79.8 ± 2.4
2c	100.5 ± 2.1	162.9 ± 3.8	109.3 ± 2.2	91.4 ± 2.4
2d	93.9 ± 1.9	128.4 ± 2.9	89.5 ± 1.7	86.1 ± 1.8
2e	313.5 ± 5.8	427.1 ± 7.9	299.1 ± 5.2	284.5 ± 4.7
2f	81.3 ± 2.1	79.6 ± 2.2	75.2 ± 2.7	71.3 ± 2.3
3a	136.9 ± 3.4	212.6 ± 4.4	126.1 ± 3.3	124.8 ± 3.1
4a	134.7 ± 3.2	217.8 ± 4.1	122.6 ± 2.9	119.7 ± 2.9
3b + **4b** (1 : 1)	189.4 ± 4.6	316.8 ± 5.1	179.4 ± 4.9	159.4 ± 5.4

of this compound. Similar effect is observed in all the synthesized pairs of compounds **2c**–**2d**, **2b**–**2f** and **2a**–**2e**. For the last pair **2a**–**2e** containing a bulky phthalimide substituent, the cytotoxicity values across all cell lines changed by a factor of 4–5.

In addition, tricyclic epoxides **2a**,**b** showed the cytotoxic activity twice as much as their bicyclic analogues **3a**,**b** and **4a**,**b**, while the regioisomeric bicycles **3a** and **4a** had the same activity in all cell lines.

In conclusion, we have synthesized new practically valuable 8-oxatricyclo[4.3.2.$0^{7,9}$]undeca-2,4,10-trienes and bicyclo[4.3.1]-deca-2,4,8-triene-7,10-diols *via m*CPBA oxidation of substituted bicyclo[4.2.2]deca-2,4,7,9-tetraenes. The obtained functionally substituted bi- and tricyclic compounds are promising as the key precursors in the synthesis of modern medicinal agents and other valuable substances. The presence of reactive functional groups in the 8-oxatricyclo[4.3.2.$0^{7,9}$]undeca-2,4,10-triene and bicyclo-[4.3.1]deca-2,4,8-triene-7,10-diol molecules opens up prospects for further targeted transformations to produce valuable compounds with specified properties. The synthesized compounds exhibited moderate cytotoxicity against Jurkat, K562, HL60, U937 tumor cell lines.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.09.013.

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