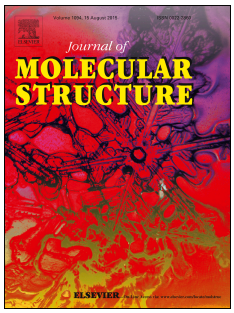
# Accepted Manuscript




The synthesis of monocyclic and bicyclic molecules and their antioxidant properties

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# The synthesis of monocyclic and bicyclic molecules and their antioxidant properties

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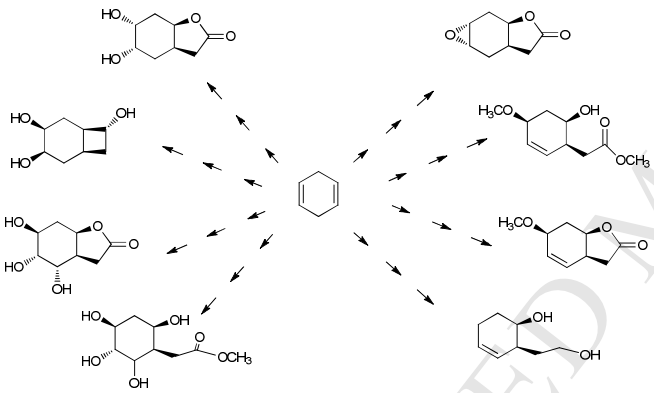
ABSTRACT

The synthesis and antioxidant activity of novel cyclitol, lactone and epoxide derivatives starting from appropriate 1.4-cyclohexadiene are reported in this study. All structures of these products were characterized by $^{1}$H-NMR, $^{13}$C-NMR, MS and IR spectroscopy. The antioxidant capacities of some synthesized compounds were studied by using the methods of the scavenging effect on DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals. It is seen that the antioxidant properties of two of the five synthesized molecules were close to α-tocopherol.

## Graphical abstract



## Keywords

Cyclitols, bicyclic molecules, lactones, epoxide, antioxidant properties, DPPH.

## Highlights

1. Hydroxyl and epoxide group containing molecules were synthesized and characterized
2. The antimicrobial activity of the synthesized compounds was evaluated.
3. A new mechanism was proposed in the synthesis of triol.

## 1. Introduction

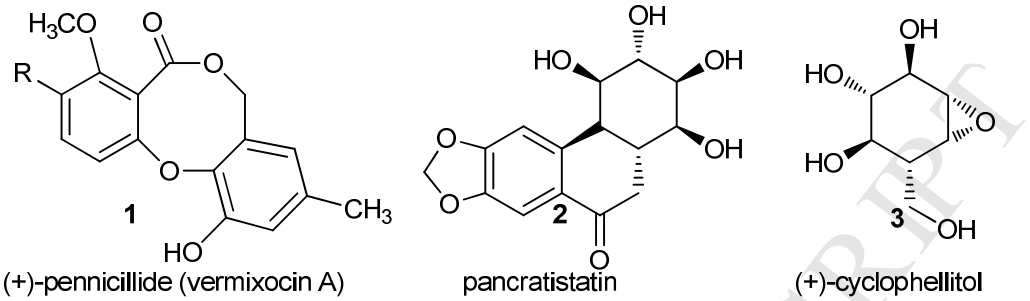



**Fig. 1.** A few examples showing biological activity

Cyclitols are sugar alcohol with one hydroxyl group on each of three or more ring atoms, which attract attention since they have many biological properties such as anticancer, antibacterial, antifungal, HIV inhibitory, enzyme inhibitory activities, etc [1-6]. Therefore, the synthesis of cyclitol derivatives also gain interest [7-14]. Some of the methyl ether inositol derivatives are plant secondary metabolites, molecules that are not directly involved in normal growth but play an important role in defense against adverse environmental conditions [15-18]. Mondal and coworkers synthesize (±)-cyclophellitol, (±)-valienamine, (±)-gabosine I, (±)-gabosine G, (±)-gabosine K, (±)-streptol, (±)-1-epi-streptol, (±)-uvamalol A, lincitol A, lincitol B, uvacalol I, uvacalol J, and uvacalol K starting from myo-inositol [19, 20]. Another example, Pennicillide derivative **1**, which is a lactone ring and methyl ether, has been shown to be an antagonist of the peptide hormone oxytocin as an inhibitor of the cholesterol ester transfer protein [20-24]. Lactones which are one of the biologically important molecules can also be used as antitumor agents [20]. Pancratistatin (**2**) is a cyclitols derivative, a phenanthridone-type natural product, which is isolated from several plants of the Amaryllidaceae family and has antiproliferative, antivascular, antiviral and antiparasitic properties [25]. Epoxy-cyclitols are also molecules with biological properties. Conduritol epoxides, and more specifically, the fungal metabolite cyclophellitol (**3**), are potent glycosidase inhibitors and are under investigation as inhibitors of HIV infection and cancer metastasis [26-28]. Numerous studies on the importance and synthesis of cyclitols are available in literature [1-31]. Due to the biological importance of cyclitols, studies on their synthesis are still popular. So in this paper, we describe a new synthetic methodology leading to the synthesis of various cyclitol derivatives having lactone, metoxy, epoxy groups and their antioxidant properties, which have been measured by the DPPH method.

## 2. Experimental section

### *2.1. General*

Infrared spectra were recorded on the Perkin Elmer Win First® Satellite. The $^{1}H$ and $^{13}C$ NMR spectra were recorded on the Bruker Ultrashield Plus Biospin GmbH 400 MHz spectrometer. Column chromatography was performed on silica gel (60-mesh, Merck), TLC was carried out on Merck 0.2 mm silica gel 60 $F_{254}$ analytical aluminum plates. All the chemicals and reagents were of analytical grade and obtained from either Sigma or Merck.

### *2.2. trans-5,6-Dibromohexahydrobenzofuran-2(3H)-one (**9**) with $H_2O_2$ (Method 1)[32]*

A solution of $H_2O_2$ (177 mg, 30%) in acetic acid (0.88 mL) was added to a solution of *trans*-3,4-dibromobicyclo[4.2.0]octan-7-one (**7**) (500 mg, 1.77 mmol) in $CH_2Cl_2$ (5 mL) and the resulting mixture was

stirred for 20 h at room temperature. After the completion of the reaction, the mixture was washed with water and saturated $NaHCO_3$. The organic phase was dried over $MgSO_4$. The residue was chromatographed on a silica gel (5 g) column eluting with ethyl acetate/hexane (1:1). At the end of the reaction only one product was obtained, identified as *trans*-5,6-dibromohexahydrobenzofuran-2(3H)-one (**9**) (449 mg, 85%) [18].

*2.3. cis-5,6-Dibromohexahydrobenzofuran-2(3H)-one(**10**)*

The experiment was performed according to method 1. As a result of the experiment *cis*-5,6-dibromohexahydrobenzofuran-2(3H)-one (**10**) was obtained with the yield of 80% (423 mg, colorless liquid).

*2.4. Reaction of cis- and trans-dibromo-lactones (**9** and **10**) with NaOMe*

463 mg Na metal (20.1 mmol) was dissolved in 30 mL methanol. 5.98 g of dibromide **9** and **10** were dissolved in 10 mL of methanol and added to the NaOMe solution, which was stirred for 24 hours. After the reaction was completed, it was purified by column chromatography via silica gel (1:4 ethyl acetate/hexane). *rac*-Methyl 6-hydroxy-4-methoxycyclohex-2-en-1-yl)acetate (**11**) with an yield of 35% (1.42 g), *rac*-methyl 4,5-dibromo-2-hydroxycyclohexyl)acetate (**12**) with an yield of 30% (1.98 g) and *rac*-6-methoxy-3,3a,7,7a-tetrahydrobenzofuran-2(6H)-one (**13**) with an yield of 20% (674 mg) were obtained.

*2.5. Typical procedure for the formation of rac-methyl 2-(6-hydroxy-4-methoxycyclohex-2-en-1-yl)acetate(**11**) with $OsO_4$/NMO oxidation (Method 2)[32]*

*rac*-Methyl2-(6-hydroxy-4-methoxycyclohex-2-en-1-yl)acetate (**11**) (500 mg, 2.5 mmol) was dissolved in a mixture of $H_2O$–acetone (10 mL, 1:1) solution and NMO (500 mg, 5.18 mmol) and then, $OsO_4$ (5 mg,0.02 mmol) in acetone (5 mL) was added to the stirring solution of molecule **11**. The mixture was stirred at room temperature for 24 h. The reaction was monitored by TLC. The solution was evaporated, and then the crude residue was directly purified by column chromatography on silica gel using EtOAc-hexane as eluent to give *rac*-methyl 2-(2,3,4,6-tetrahydroxycyclohexyl)acetate (**16**) (385 mg, 70%).

*4.6 rac-4,5,6-Trihydroxyhexahydrobenzofuran-2(3H)-one (**17**)*

The experiment was performed according to method 2. As a result of the *rac*-4,5,6-trihydroxyhexahydrobenzofuran-2(3H)-one (**17**) was obtained with the yield of 80% (448 mg, colorless liquid).

*4.7 rac-2-(2-hydroxyethyl)cyclohex-3-enol(**18**) [32]*

To a magnetically stirred slurry of 2 eq. $LiAlH_4$ (127 mg, 3.35 mmol) in 100 mL of ether was added a solution of methoxy lactone **13** (500 mg, 2.97 mmol) in ether (50 mL) dropwise at 0 ℃ for over 2 h. The mixture was stirred at room temperature for 5 h. Then the reaction mixture was cooled to 0 ℃ and cold water was added and it was filtered through silica gel (20 g). The organic layer was dried over $MgSO_4$ and the solvent was removed. The residue was chromatographed on a silica gel (30 g) column eluting with diethyl ether/hexane (3:1). *rac*-2-(2-hydroxyethyl)cyclohex-3-enol (**18**) was obtained at the end of the reaction (296 mg, 70%, colorless liquid)

*4.8 rac-Tetrahydrobenzofuran-2(3H)-one (**19**)*

The experiment was performed according to method 1. As a result of the experiment tetrahydrobenzofuran-2(3H)-one (**19**) was obtained with the yield of 60% (339 mg, colorless liquid).

*4.9 rac-Hexahydrooxireno[2,3-f]benzofuran-4(1aH)-one (**20**) [33]*

Tetrahydrobenzofuran-2(3H)-one (**19**) (500 mg, 3.62 mmol) was dissolved in 150 mL of chloroform, 1 eq. (624.7 mg, 3.62 mmol) 70% *m*-CPBA was added, and then the reaction was stirred at room temperature for 24 h. The reaction mixture was added to 15 mL of 50% $NaHSO_3$ solution and the mixture was stirred for 15 min. The organic layer was separated and then washed with saturated aqueous $NaHCO_3$ (100 mL), dried with $MgSO_4$ and concentrated to give *rac*-hexahydrooxireno[2,3-f]benzofuran-4(1aH)-one (**20**) (385 mg, 69%).

*4.10 rac-5,6-Dihydroxyhexahydrobenzofuran-2(3H)-one(**21**)*

The experiment was performed according to method 2. As a result of the *rac*-5,6-dihydroxyhexahydrobenzofuran-2(3H)-one (**21**) was obtained with the yield of 75% (467.4 mg, colorless liquid).

4.11 *Bicyclo[4.2.0]oct-3-en-7-ol (**22**)*

2 g (16.4 mmol) of starting material **6** is dissolved in 100 mL methanol solution and $NaBH_4$ (620 mg, 10.8 mmol) is slowly added (2 min) by stirring. The mixture is allowed to react for 24 h. The residue was chromatographed on a silica gel (30 g) column eluting with diethyl ether/hexane (1:1). Bicyclo[4.2.0]oct-3-en-7-ol (**22**) was obtained with the yield of 60% (1.22 g, colorless liquid) at the end of the experiment.

*4.12 Bicyclo[4.2.0]octane-3,4,7-triol (**23**)*

The experiment was performed according to method 2. As a result of the bicyclo[4.2.0]octane-3,4,7-triol (**23**) was obtained with the yield of 75% (448 mg, colorless liquid).

4.13 *Antioxidant activities, Scavenging effect on DPPH radicals [34]*

1 mL of the methanol extract in arrange of concentrations (0.03–0.5 mg/mL) was added to 1mL of DPPH radical solution in methanol (the final concentration of DPPH was 0.2 mM). The mixture was shaken vigorously and kept to stand for 30 min in the dark, and the absorbance was measured at 517 nm against a blank using the Elisa Reader. Ascorbic acid, Gallic acid, BHT and α-tocopherol were used as standard controls. The inhibition of DPPH free radicals was calculated in percentages via the following equation.

$$I\% = (A_{blank}-A_{sample}) / A_{blank} \times 100$$

Where $A_{blank}$ is the absorbance of the control reaction, and $A_{sample}$ is the absorbance of the test compound. The extract concentration providing 50 % inhibition ($IC_{50}$) was calculated from a graph plotting inhibition percentage against extract concentration. Tests were performed in triplicate.

## 4. Result and discussion

Bicyclic ketone **6,** the key compound of the synthesis, can be easily synthesized via ketene addition to 1,4-cylohexadiene (**4**) described by Kishalı [10]. Later, *trans*- and *cis*-dibromide (**7**, **8**) were obtained at 0 ℃ as a result of the bromination of bicyclic ket one **6** which were separated by column chromatography (Fig. 2) [35]. *trans*-Isomer **7** (Rf=0.95) has a larger Rf value than *cis*-isomer **8** (Rf=0.83) [hexane/ ethyl

acetate mixture (9:1)]. *trans*-Dibromide **7** was formed as the major product with 60% yield. The absorption bands at 1774 $cm^{-1}$ (**8**) and 1779 (**7**) in the FT-IR spectra confirmed the cyclobutanone ring in the structure. In molecule **7**, $H_4$ and cyclobutanone rings are in a different space. Because there is no w-interaction as a Cosy spectrum; but $H_3$ and cyclobutanone rings are in the same space since there is a w-interaction as a Cosy spectrum. In molecule **8**, $H_3$ did not give a w-interaction with $H_1$ and $H_4$ did not give a w-interaction with the $H_6$ proton. This shows that the bromines are in *cis*-position relative to each other and in the *trans*-position relative to the cyclobutanone ring. In the next step, the oxidation of *trans- and cis*-dibromide **7** and **8** with $H_2O_2$ were made and *trans*-dibromolactone **9** with 85% yield and *cis*-dibromo lactone **11** were obtained with 80% yield (Fig. 2). There is the signal of carbonyl carbonof *trans*-dibromo lactone **9** in 175.4 ppm and the signal of carbonyl carbon of *cis*-dibromo lactone **10** 175.0 ppm in the $^{13}C$ NMR spectrum of lactone.

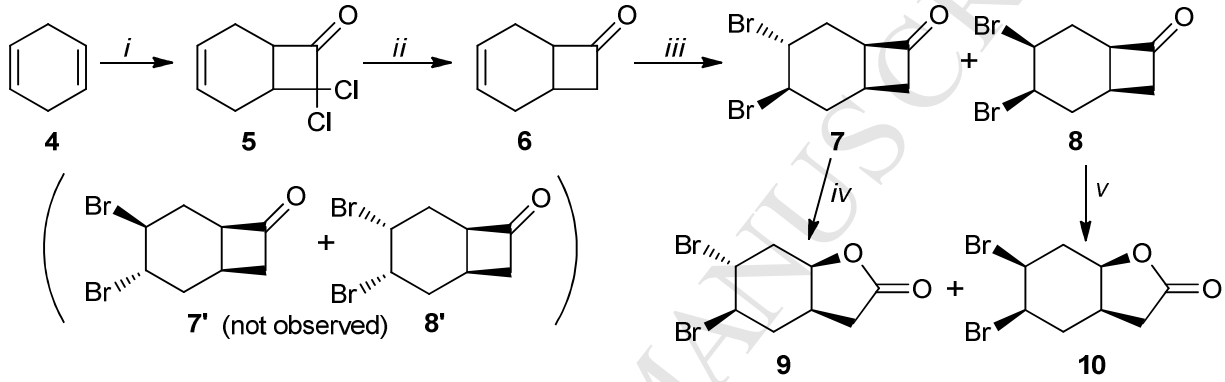



**Fig 2.** *Reagents and conditions:* (*i*) $Cl_3CCOCl$, Zn, $POCl_3$, ether, 25 $^oC$, 87%; (*ii*) Zn, $CH_3COOH$, 92%; (*iii*) $Br_2$, $CHCl_3$, 0 $^oC$, 60% *trans*, 30% *cis*; (*iv*) $H_2O_2$, $CH_2Cl_2$, 85%, (*v*) $H_2O_2$, $CH_2Cl_2$, r.t., 80% [17].

The reaction of *trans*- and *cis*-dibromo lactone **9** and **10** with excess of NaOMe gave three products (**11**-**13**) (Fig. 3). All NMR data of the synthesized molecules (**11**-**13**) were in agreement with the proposed structure. The w-interaction between $H_4$ and $H_6$ is clearly seen in the Cosy spectrum molecule **11**. This proves that the position of the groups relative to each other is *cis*. The $H_5$ and the $H_1$ are in *trans*-position relative to each other, since there is no w-interaction between $H_1$ and $H_5$ in molecule **12** according to the Cosy spectrum. They are in the *cis*-position of each other in $H_4$ and $H_2$ because there is w-interaction between $H_2$ and $H_4$ in molecule **12** according to the Cosy spectrum. In molecule **13**, the $H_6$ and $H_8$ are are in *cis*-position relative to each other, because of w-interaction between $H_6$ and $H_8$.

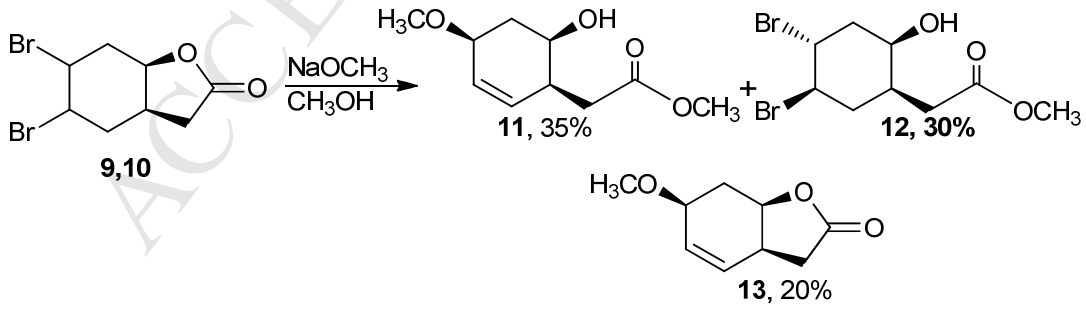



**Fig 3.** The reaction of *trans*- and *cis*-dibromo lactone **9** and **10** with NaOMe [18].

After the successful purification and characterization of the cyclitol derivatives **11**-**13**, molecule **11** reacted with a catalytic amount of $OsO_4$ in the presence of 2 eq. NMO as co-oxidant (Fig. 4) and

unexpected product tetrol **16** was obtained. We assume that molecule **16** was obtained via well-known $S_Ni$ reaction. First, the $OsO_4$ addition reaction occurred, and then the five-atom ring was opened via $S_Ni$ reaction. Molecule **16** was consistent over intermediate **15**. As a result, the direction of the hydroxyl groups is also in the *trans*position relative to the other groups. As protons $H_{4'}$ and $H_{6'}$ overlap, we cannot comment on these protons for compound **16**. But, the absence of w-interaction between $H_{1'}$ and $H_{3'}$ indicates that these protons are *trans*. The absence of w-interaction between $H_{2'}$ and $H_{4'}$ again indicates that these protons are *trans*. As a result, we can say that $H_{3'}$ and $H_{1'}$ (again $H_{4'}$ and $H_{2'}$) are in *trans* position.

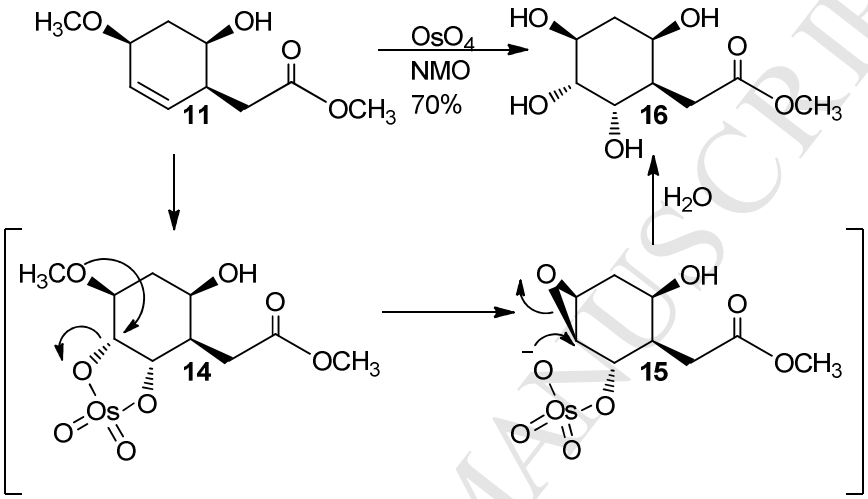



**Fig. 4.** The synthesis of tetrol**16** and the reaction of molecule**11** with $OsO_4$/NMO

The *cis*-hydroxylation reaction of the methoxy lactone **13** was carried out. As in molecule **11**, $S_Ni$ reaction was observed in this reaction and triol-lactone **17** was obtained (Fig. 5). As a result, the direction of the hydroxyl groups ($C_4$-OH and $C_5$-OH) is also in the *trans* position relative to the other group ($C_6$-OH and lactone ring). Furthermore, $H_5$ does not interact with $H_9$, based on the Cosy spectrum of molecule **17**. In addition, $H_4$ does not interact with $H_8$.

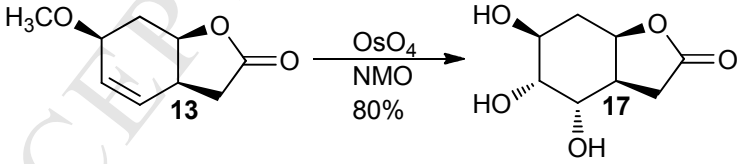



**Fig. 5.** The synthesis of triol-lactone **17**

The reaction of the methoxylactone **13** with $LiAlH_4$ resulted in a surprising product (Fig. 6). As a result of the reaction, the lactone reaction was followed by a substitution reaction with hydride. In the end, diol **18** was obtained from methoxylactone **13**.

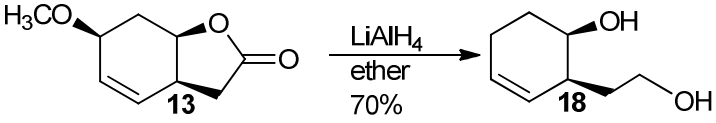



**Fig. 6.** The synthesis of diol **18**

On the other hand, bicyclic ketone **6** was converted to bicyliclactone **19** in 60% yield with $H_2O_2$ (Fig. 7). Bicyclic lactone **19** reacted with *m*-CPBA, epoxy lactone **20** was obtained with 69% yield (Fig. 7). If the epoxide and lactone rings are in the *trans* position, the hydrogen of the epoxide ring gives the triplet signal. When we look at the $^1$H NMR spectrum, we see that one of the hydrogens of the epoxide ring gives triplet and the other gives a close signal to triplet. In addition, the absence of the w-interaction between the $H_5$-$H_9$ and $H_6$-$H_8$ in the Cosy spectrum also confirms the structure. The same is applied to molecule **21**.

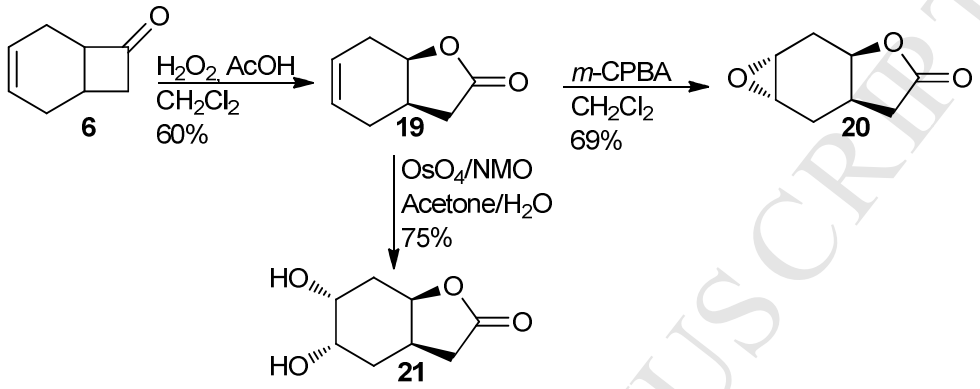



**Fig. 7.** The synthesis of molecules**20** and **21**

Finally, the reaction of bicyclic ketone **6** with $NaBH_4$ and bicyclic alcohol **22** was obtained with 60% yield (Fig. 8). The reaction of bicyclic ketone with $OsO_4$/NMO gave bicyclic triol **23** with 75% yield (Fig. 8). In triol **23**, hydroxyl groups are in different space with cyclobutanone, because there is no w-interaction between $H_3$ and $H_1$, and at the same time $H_4$-$H_6$. This is also applied to $H_4$ and $H_6$. The absence of the w-interaction between $H_{5a}$ and $H_{5b}$ with $H_7$ proves to be in the same space as the hydroxyl groups.

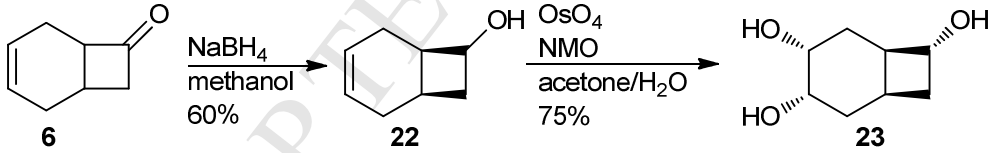
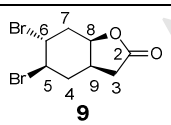
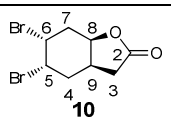
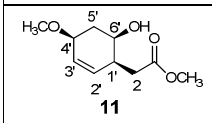
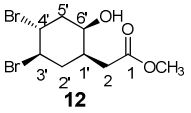
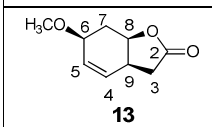
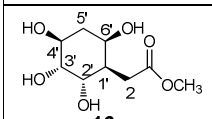
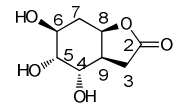
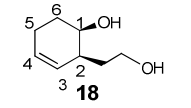
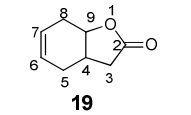
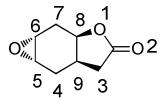
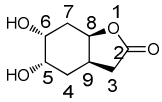
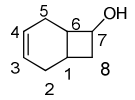
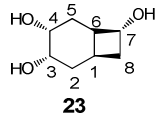



**Fig. 8.** The synthesis of bicyclic triol **23**

**Table 1.** Spectral data of synthesized molecules

| | FTIR | $^1$HNMR | $^{13}$C NMR | GCMS | ELEMENTEL |
|---|---|---|---|---|---|
|  **9** | 2961, 2919 (-C-H), 1761 (-C=O) | 4.68 (m, $H_8$, 1H), 4.64 (m, $H_6$, 1H), 4.5 (m, $H_5$, 1H), 2.87 (m, $H_9$, $H_{7a}$, $H_{4a}$ and $H_{7b}$, 4H), 2.46 (m, $H_{3a}$, 1H), 2.36 (d, $H_{4b}$, 1H, *J*= 17.01 Hz), 2.09 (dt, $H_{3b}$, 1H, *J*= 15.25, 4.43 Hz) | 175.4, 75.4, 50.1, 44.3, 36.7, 30.9, 29.9, 29.1 | 297.8, ($M^+$, -Br), 217, ($M^+$, -Br), 137, ($M^+$, -COO) | $C_8H_{10}Br_2O_2$, C, 32.25, H, 3.38%, found: C, 32.23, H, 3.40% |
|  **10** | 2923 (-CH) 1764 (-C=O) | 4.62 (m, $H_8$, 1H), 4.31 (m, $H_6$, 1H), 4.17 (m, $H_5$, 1H), 2.98 (dt, $H_{7a}$, 1H, *J*=15.3 and 34.1), 2.67 (m, $H_{3a}$, $H_{4a}$, $H_9$, 3H), 2.52 (d, $H_{3b}$, 1H, *J*= 14.74 Hz), 2.32 (m, $H_{7b}$, 1H), 2.01 (m, $H_{4b}$, 1H) | 175.0, 77.8, 51.5, 49.9, 37.2, 36.6, 36.4, 35.3 | 302.9, ($M^+$, -OH), 284, 283, 282 ($M^+$, -$CH_2CH_2$), 258, 257, 256, 255, 254, ($M^+$, -Br) 176, 175, 174, 173, ($M^+$, -OH) | $C_8H_{14}Br_2O_2$, C, 31.82, H, 4.67%, found: C, 31.84, H, 4.65% |

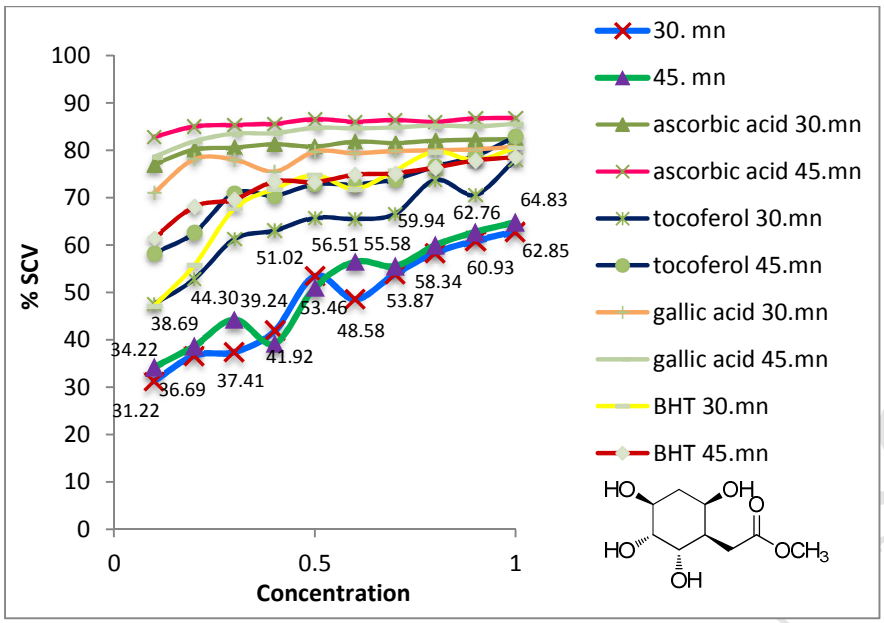
| | | | | | |
|---|---|---|---|---|---|
| | | | | 160, 159, 158, 157, ($M^+$, -Br) 80, 79, 78, 77 | |
|  **11** | 3435 (-OH) 2955, 2926 (-C-H), 1730 (-C=O) | 5.88 (m, $H_{2'}$, 1H), 5.79 (m, $H_{3'}$, 1H), 3.92 (m, $H_{6'}$, 1H), 3.70 (s, -$OCH_3$), 3.64 (m, $H_{4'}$, 1H), 3.46 (s, -$OCH_3$), 2.63 (dd, $H_{2a}$, 1H, *J*= 15.3, 5.1 Hz), 2.47 (m, $H_{1'}$, 1H), 2.34 (dd, $H_{2b}$, 1H, *J*= 15.3 2 Hz), 2.21 (bd, $H_{5a'}$, 1H), 2.04 (bd, $H_{5b'}$, 1H) | 173.7, 129.9, 123.6, 78.1, 70.2, 56.6, 51.6, 34.8, 32.3, 27.9 | 200.9, ($M^+$, -$CO_2CH_3$), 146 (M+, -$CH_3$), 132.8 ($M^+$, -O, -OH) | $C_{10}H_{16}O_4$, C, 59.98, H, 8.05%, found: C, 59.87, H, 8.09% |
|  **12** | 3458 (-OH) 2921 (-C-H), 1719 (-C=O) | 4.33 (m, $H_{4'}$, 1H), 4.02 (m, $H_{3'}$, 1H), 3.91 (m, $H_{6'}$, 1H), 3.62 (s, -$OCH_3$), 2.55 (dt, $H_{5'a}$, 1H, *J*= 14.2, 4.3 Hz), 2.39 (dd, $H_{2'a}$, 1H, *J*= 15.7, 7.7 Hz), 2.25 (dd, $H_{2'b}$, 1H, *J*= 15.7, 6.0 Hz), 2.16 (m, $H_{1'}$ and $H_{2a}$, 2H), 2.02 (m, $H_{5'b}$ and $H_{2b}$) | 172.8, 68.6, 55.8, 52.7, 51.9, 44.8, 38.9, 37.7, 36.3 | 330 ($M^+$, -$OCH_3$), 300 ($M^+$, -C=O, -Br), 196 ($M^+$, -Br) | $C_9H_{14}Br_2O_3$, C, 32.76, H, 4.28%, found: C, 32.72, H, 4.25% |
|  **13** | 2929 (-CH), 1774 (-C=O) | 5.93 (m, $H_5$, 1H), 5.84 (dt, $H_4$, 1H, *J*= 10.1, 2.5 Hz), 4.58 (dd, $H_8$, 1H, *J*= 6.7, 3.59 Hz), 3.83 (m, $H_6$, 1H), 3.47 (s, -$OCH_3$, 3H), 2.72 (dd, $H_{3a}$, 1H, *J*= 16.8, 8.6 Hz), 2.64 (m, $H_9$, 1H), 2.36 (m, $H_{3b}$, 1H), 2.25 (dd, $H_{7a}$, 1H, *J*= 12.6, 4.1 Hz), 1.87 (m, $H_{7b}$, 1H) | 176.2, 128.2, 126.8, 82.7, 75.9, 57.2, 35.5, 31.4, 26.6 | 168 ($M^+$, -$CH_3$), 153 ($M^+$, -O), 153 ($M^+$, -$CO_2$), 109 | $C_9H_{12}O_3$, C, 64.27, H, 7.19%, found: C, 64.19, H, 7.21% |
|  **16** | 3344 (-OH), 2923, 2852 (-CH), 1765 (-C=O) | 4.63 (t, $H_2$, 1H, *J*= 5.79 Hz), 3.94 (t, $H_4$, 1H, *J*= 2.91 Hz), 3.9 (m, $H_6$, 1H), 3.55 (s, -$OCH_3$, 3H), 3.53 (m, $H_3$, 1H), 2.84 (m, $H_1$, 1H), 2.6 (dd, $H_{2a'}$, 1H, *J*= 17.19, 7.7 Hz), 2.3 (dd, $H_{2b'}$, 1H, *J*= 17.19, 6.62 Hz), 2.08 (m, $H_{5a}$, 1H), 1.65 (ddd, $H_{5b}$, 1H, *J*= 14.36, 7.61, 3.85 Hz) | 175.6, 80.5, 80.2, 68.7, 68.1, 59.1, 35.1, 30.5, 30.2, 29.9 | 220.2 ($M^+$, -OH), 205.2 ($M^+$, -$OCH_3$, -3OH), 126.1 ($M^+$, -CO), 112.1 | $C_9H_{16}O_6$: C, 49.09, H, 7.32%. Found: C, 49.07, H, 7.30% |
|  **17** | 3393 (-OH), 2925 (-CH), 1723 (-C=O) | 4.08 (m, $H_9$, 1H), 3.87 (m, $H_5$ and $H_6$, 2H), 3.66 (t, $H_4$, 1H, *J*= 3.18 Hz), 2.55 (dd, $H_{1a}$, 1H, *J*= 15.6, 7.2 Hz), 2.36 (dd, $H_{1b}$, 1H, *J*= 15.6, 6.8 Hz), 2.26 (m, $H_8$, 1H), 1.61 (m, $H_{7ab}$, 2H) | 173.4, 79.6, 71.2, 69.6, 68.1, 36.5, 32.9, 28.8 | 185.1 ($M^+$, -CO), 157.1 ($M^+$, -$CH_2$, -O), 111.1 ($M^+$, -OH), 95.1, ($M^+$, -OH), 79.1 | $C_8H_{12}O_5$: C, 51.06, H, 6.43%. Found: C, 51.07, H, 6.45% |
|  **18** | 2929, 2847 (-CH), 1715 (-C=O) | 5.86 (m, $H_5$, 1H), 5.76 (m, $H_6$, 1H), 4.83 (td, $H_{3a'}$, 1H, *J*= 9.34, 3.3 Hz), 2.8 (dd, $H_{1a}$, 1H, *J*= 17.1, 7.9 Hz), 2.71 (m, $H_{7a'}$, 1H), 2.51 (m, $H_{7a}$, 1H), 2.41 (m, $H_{4a'}$, 1H), 2.3 (dd, $H_{1b}$, *J*= 17.0, 3.81 Hz), 1.92 (m, $H_{4b'}$, 1H), 1.33 (d, $H_{7b}$, *J*= 14.9 Hz) | 179.8, 127.2, 125.1, 79.8, 37.9, 33.4, 28.3, 27.2 | 138.1 ($M^+$, -C=O), 110.1 ($M^+$, -OH), 96.1, | $C_8H_{10}O_2$: C, 69.54, H, 7.30%. Found: C, 69.59, H, 7.34% |
|  **19** | 2929, 2847 (-CH), 1715 (-C=O) | 5.86 (m, $H_5$, 1H), 5.76 (m, $H_6$, 1H), 4.83 (td, $H_{3a'}$, 1H, *J*= 9.3, 3.3 Hz), 2.8 (dd, $H_{1a}$, 1H, *J*= 17.1, 7.9 Hz), 2.71 (m, $H_{7a'}$, 1H), 2.41 (m, $H_{4a}$, 1H), 2.3 (dd, $H_{1b}$, 1H, *J*= 17.0, 3.8 Hz), 1.92 (m, $H_{4b}$, 1H), 2.51 (m, $H_{7a}$, 1H), 1.33 (d, $H_{7b}$, 1H, *J*= 14.9 Hz) | 179.8, 127.2, 125.1, 79.8, 37.9, 33.4, 28.3, 27.2 | 138.1 ($M^+$, -O), 124.1, ($M^+$, -C), 112, ($M^+$, -O), 96.0 | $C_8H_{10}O_2$: C, 69.54, H, 7.30%., C 69.55, H, 7.37% |

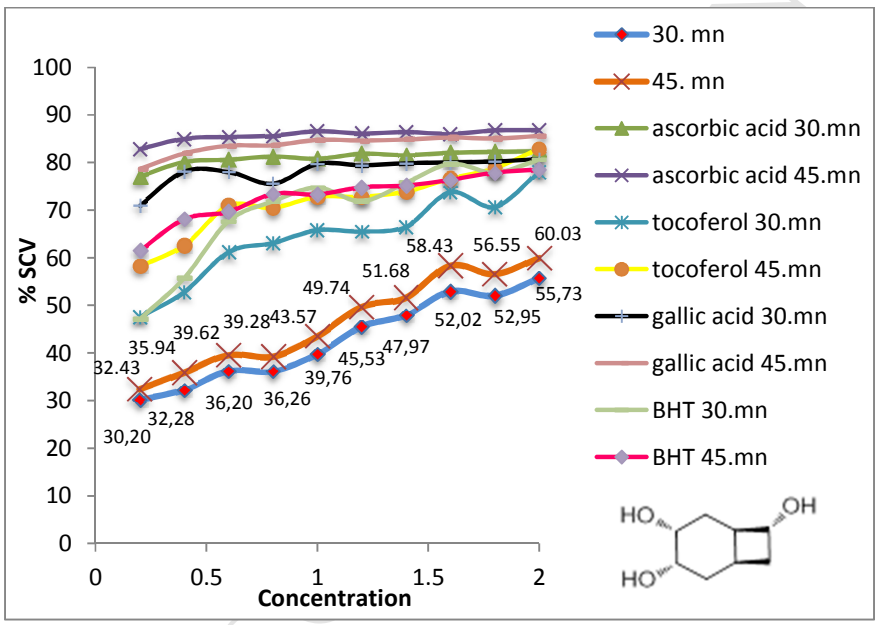
| | | | | | |
|---|---|---|---|---|---|
|  **20** | 3005, 2942 (-CH),1763 (-C=O), | 4.57 (t, $H_8$, 1H), 3.27 (t, $H_6$, 1H, *J*= 3.6 Hz), 3.21 (m, $H_5$, 1H), 2.72 (m, $H_9$, 1H), 2.68 (m, $H_{3a}$, 1H), 2.6 (ddd, $H_{7a}$, 1H, *J*= 16.7, 7.8, 1.8 Hz), 2.3 (m, $H_{3b}$, $H_{4a}$ and $H_{7b}$, 3H), 1.79 (dd, $H_{4b}$, 1H, *J*= 15.1, 9.9 Hz) | 176.0, 75.7, 51.0, 49.3, 36.5, 30.0, 26.2, 25.7 | 154.0 ($M^+$, -C=O), 126.0 ($M^+$, -O), 114 ($M^+$, $-CH_2$) 84, | $C_8H_{10}O_3$: C, 62.33, H, 6.54%. Found: C, 62.35, H, 6.57% |
|  **21** | 3376, 3257 (-OH), 2963, 2899 (-CH), 1766 (-C=O), | 4.73 (m, $H_5$, 1H), 3.92 (m, $H_6$, 1H), 3.72 (m, $H_8$, 1H), 3.34 (m, $H_9$, 1H), 2.81 (dd, $H_{3a}$, 1H, *J*= 16.4, 1.9 Hz), 2.66 (m, $H_{7a}$, 1H), 2.23 (dd, $H_{3b}$, 1H, *J*= 16.9, 1.2 Hz), 2.1 (m, $H_{7b}$, 1H), 2 (dt, $H_{4a}$, 1H, *J*= 14.5, 5.4 Hz), 1.38 (m, $H_{4b}$, 1H) | 179.7, 69.1, 67.8, 81.9, 31.6, 48.8, 33.2, 30.7 | 172.0 ($M^+$, -OH), 154.0 ($M^+$, -C=O), 112 ($M^+$, $-CH_2$) 95 | $C_8H_{12}O_4$: C, 55.81, H, 7.02%. Found: C, 55.79, H, 7.04% |
|  **22** | 3322 (-OH), 2966, 2926, 2830 (-CH), | 6.01 (m, $H_3$, 1H), 5.74 (m, $H_4$, 1H), 4.22 (m, $H_7$, 1H), 2.67 (m, $H_6$, 1H), 2.43 (m, $H_{8a}$, 2H), 2.26 (m, $H_{5ab}$, 2H), 2.03 (m, $H_{2ab}$, 2H), 1.85 (m, $H_1$, 1H), 1.62 (m, $H_{8b}$, 2H | 127.7, 126.6, 65.8, 37.4, 23.5, 37.2, 26.4, 18.5 | 122 ($M^+$, -OH), 108 | $C_8H_{12}O$: C, 77.38, H, 9.74%. Found: C, 77.37, H, 9.72% |
|  **23** | 3337 (-OH), 2907, 2868, 2804 (-CH), | 4.15 (m, $H_7$, 1H), 3.9 (m, $H_4$, 1H), 3.73 (ddd, $H_3$, 1H, *J*= 11.4, 5.2, 2.0 Hz), 2.52 (m, $H_6$, 1H), 2.17 (m, $H_{8a}$, 1H), 2.09 (m, $H_1$, 1H), 2.02 (s, $H_{5a}$, 1H), 1.96 (m, $H_{5b}$, 1H), 1.88 (m, $H_{8a}$, 1H), 1.77 (m, $H_{2a}$, 1H), 1.54 (dd, $H_{2b}$, 1H, *J*= 13.3, 5.2 Hz) | 70.3, 70.2, 65.3, 36.3, 34.7, 29.0, 27.0, 25.7, 20.8 | 158.1 ($M^+$, 3-OH), 110.1 | $C_8H_{14}O_3$: C, 60.74, H, 8.92%. Found: C, 60.70, H, 8.89% |

**Antioxidant potential**

The DPPH radical scavenging effects of five synthesized molecules (**16**, **17**, **18**, **20**, and **23**), along with those of ascorbic acid, gallic acid, BHT, α–tocopherol controls, rose with the increased concentration from 0.1 mL to 1 mL (Table 2) [35].If we look at the% SCV of **16** and **23**, we will see that the antioxidant property of molecules **16** and **23** at 45 minutes is close to α-tocopherol. There are studies in literature that some cyclitol derivatives have antioxidant properties. Our study supports these studies [36,37].

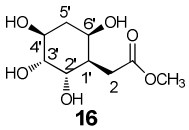
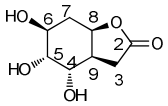
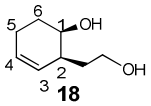
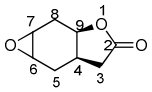
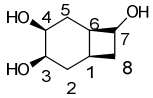
**Table 2.** % SCV graphic against concentration of molecules **16** and **20**




The scavenging values are 0.59 mg/mL for *tetrol* **16**, 5.46 mg/mL for triol **17**, 4.94 mg/ml for diol **18**, 1.4 mg/mL for epoxide **20**, 1.57 mg/mL for triol **23**, 6.6 mg/mL for ascorbic acid, 3.2 for gallic acid, 8,8. $10^{-2}$ mg/mL for BHT and 4,4.$10^{-3}$ mg/mL for α-tocoferol for 30 min. (Table 2). Antioxidant results of several of the synthesized compounds with respect to ascorbic acid, gallic acid, BHT, and α-tocopherol were reported in Table 3.

Table 3. $IC_{50}$ values of some synthesized molecules in the DPPH

| | $IC_{50}$ (mg/mL) | |
|---|---|---|
| | 30 min. | 45 min. |
|  **16** | 0.59 | 0.53 |
|  **17** | 5.46 | 4.9 |
|  **18** | 4.94 | 4.14 |
|  **20** | 1.4 | 1.36 |
|  **23** | 1.57 | 1.3 |
| Ascorbic Acid | 6.6 | 10.62 |
| Gallic Acid | 3.2 | 5.2 |
| BHT (Butylated hydroxytoluene) | $8{,}8.10^{-2}$ | 0.9 |
| α-tocopherol | $4{,}4.10^{-3}$ | 0.4 |

## 5. Conclusion

In the study, we developed a route for the synthesis of cyclitol, lactone and epoxide derivatives starting from appropriate 1,4-cyclohexadiene.The synthesis was carried out by a series of reactions such as the addition of dichloroketene to one of the double bonds in 1,4-cyclohexadiene, the reduction of a ketene addition product and the epoxidation and *cis*-hydroxylation of double bond. Consequently, monocyclic, bicyclic diol, triol, tetrol, bicyclic lactones and bicyclic epoxide were obtained, which were likely to show biological activity. In addition, the antioxidant properties of five molecules (**16**, **17**, **18**, **19**, and **22**) were measured and compared with standards (Ascorbic acid, Gallic acid, BHT, α-tocopherol).In conclusion, it was observed that the antioxidant properties of the two cyclitols (**16** and **20**) were close to α-tocopherol.

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