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# Some Prenylated Phenols of *Rhododendron Adamsii:* Isolation, Modification and Pharmacological Tests

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## Abstract

Methyl ester of cannabigerorcynic acid **1,** a derivative of octahydroxanthenol **2** unknown earlier and daurichromenic acid **4** were isolated from the lipophilic extracts of *Rh. Adamsii.* Derivatives have been obtained from compounds **1** and **2**. It has been demonstrated that xanthenol **2** exerts coagulating and hypothermic effects. Methyl ester of cannabigerorcynic acid has been for the first time revealed in a naturally occurring object.

**Key words:** *Rhododendron adamsii*, meroterpenoids, xanthenols, coagulants

### INTRODUCTION

*Rhododendron adamsii* represents a bush of the heather family (Ericaceae) growing in the territory of Eastern Siberia and Mongolia. This plant is used in folk medicine as a stimulating, tonic, adaptogenic remedy [1]. Earlier we investigated chemical composition of this plant [2]. In the present work we have described the components of lipophilic extracts obtained from *Rhododendron adamsii* such as methyl ester of cannabigerorcynic acid **1**, 1-(3-methylbutanoyl)-1a,4a,7-trimethyl-1,1a,1a$^1$,2,3,4,4a,9b-octahydrocyclobuta[kl]-xanthene-9-ol **2** we did not revealed in the literature, as well as daurichromenic acid **4**.

### RESULTS AND DISCUSSION

Compounds **1** and **2** (Fig. 1) were obtained via the chromatographic separation of hexane extract of *Rh. adamsii* leaves on silica gel. Using the method of HPLC we have demonstrated that these substances are present in stems of the plant, being, however, in much lower amounts. In this connection in order to turn out the aforementioned compounds we used *Rhododendron adamsii* leaves.

According to data obtained by means of high resolution mass spectrometry (HR-EI-MS), compounds **1** and **2** could be described by mo-

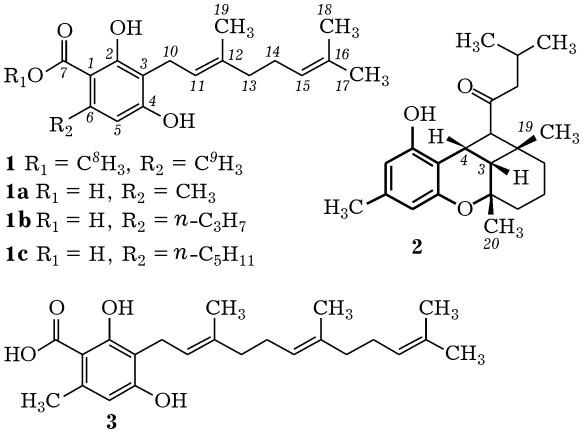



Fig. 1. Methyl ester of cannabigerorcinic acid **1**, cannabigerorcinic acid **1a**, cannabigerovarinic acid **1b**, cannabigerolic acid **1c**, 1-(3-methylbutanoyl)-1a,4a,7-trimethyl-1,1a,1a$^1$,2,3,4,4a,9b-octahydrocyclobuta[kl]-xanthene-9-ol **2** and grifolic acid **3**. Semiboldface lines designate $C_{11}H_{11}O_2$ fragment.

lecular formulas $C_{19}H_{26}0_4$ and $C_{22}H_{30}O_3$, respectively. The structure of substance **1** has been established basing on the analysis of $^1H$ and $^{13}C$ NMR spectra with the use of $^1H-^{13}C$ heteronuclear correlation spectra for direct spin-spin coupling constants. We also used one-dimensional and two-dimensional $^{13}C-^1H$ heteronuclear correlation spectra for long-range spin-spin coupling constants (SSCC). The arrangement presented for substituents in the aromatic fragment is confirmed by calculations of chemical shift values for $C^5H$ hydrogen atom in $^1H$ NMR spectrum and $C^1-C^6$ carbon atoms in $^{13}C$ NMR spectrum, which calculations were carried out taking into account additive influence of substituents. The (*E*) configuration of $C^{11}-C^{12}$ bond was determined basing on characteristic chemical shifts for $C^{13}$ *и* $C^{19}$ carbon atoms in $^{13}C$ NMR spectrum. Table 1 demonstrates chemical shift values for carbon atoms in $^{13}C$ NMR spectra of isolated compounds as well as their derivatives.

It should be noted that cannabigerorcynic acid (CGA, **1a**) as well as whatever its derivatives were not found out in natural objects earlier. The authors of [3] described the synthesis of CGA, containing a $^{14}C$ radioactive label within $C^7$ carboxyl group in order to study the biosynthesis and a metabolism of cannabinoid acids in the presence of proteins from *Cannabis sativa* [4]. Nevertheless, a number of natural compounds structurally similar to compound **1** have been already obtained earlier. So, cannabigerovarinic acid **1b** and cannabigerolic acid **1c** were isolated from *Cannabis sativa*, grifolic acid **3** was revealed in fungi belonging to genus *Albatrellus* [5]. It is known that many higher plants, in particular, the representatives of genuses *Cannabis* and *Rhododendron* use to form mycorrhiza, *i.e.* these plants exhibit symbiosis with fungi for exchanging metabolites [6]. The fungi belonging to genus *Albatrellus* wherein grifolic acid **3** has been revealed tends to form mycorrhiza, too [7], therefore prenylated phenolic compounds **1a–c** and **3**, to all appearance, represent the metabolites of symbiotic fungi. However, this assumption requires for a detailed examination as well as for carrying out additional investigations.

Methyl ester **1** at the dozes of 50 and 100 mg/kg with intragastric introduction has not demonstrated any effect in pharmacological tests concerning the determination of antioxidative and hepatoprotective activities (in the model of toxic $CCl_4$ hepatitis) as well as anti-inflammatory activity (in the model of histamine inflammation).

Compound **2** has been obtained in the form of yellow oil. The analysis of $^1H$ NMR spectra (with the use of $^1H-^1H$ double resonance spectra if necessary) has allowed us to identify the following fragments: two $CH_3$ groups at saturated carbon atoms, isopropyl group, methyl group in the aromatic nucleus, tetrasubstituted aromatic ring with *meta*-positioned protons, aromatic OH group, three CH groups linked in series, a chain consisting of three $CH_2$ groups. The $^1H-^1H$ double resonance spectra demonstrate the following series of interactions: with the suppression of the signal from aromatic $CH_3$ group exhibiting the chemical shift of 2.21 ppm the signals from benzene ring protons are narrowed to be observed as doublets with the SSCC ~ 1.5 Hz which indicates the location of $CH_3$ group between the mentioned atoms. The signals from protons of two CH groups exhibit only a doublet splitting by the proton of the third CH group with SSCC = 9.3 Hz, which could be, to all appearance, caused by the absence of neighbouring CH and $CH_2$ groups. The values of spin-spin coupling constants for the three $CH_2$ groups linked in series are inherent in axially and equatorially located protons of the cyclohexane ring, thus the aforementioned fragment represents a part of such a ring.

Data obtained from $^{13}C$ NMR spectra (including $^{13}C-^1H$ COSY two-dimension spectrum) have allowed us to determine the exact number of $CH_3$, $CH_2$, CH groups and quaternary carbon atoms (among the latter one could identify C=O group with the chemical shift value of 213.47 ppm, two carbons of the aromatic ring bonded with oxygen atoms, with chemical shift values amounting to 152.90 and 154.29 ppm and one "saturated" carbon atom bonded with oxygen, at 74.95 ppm); these data have also allowed us to reveal correlation between carbon atoms and hydrogen. Basing on the data obtained from $^{13}C-^1H$ correlation spectra for long-range SSCC (COLOC, LRJMD) we have established correlation relationships for the compound under investigation those being

TABLE 1

Chemical shift values and signal type for carbon atoms in $^{13}C$ NMR spectra of compounds **1**, **2** and their derivatives

| Number of atom | **1** | **1d** | **1e** | **2** | **2a** | **2b** | **2c** | **2d** |
|---|---|---|---|---|---|---|---|---|
| *1* | 105.02 s | 123.93 s | 124.51 s | | | | | |
| *2* | 162.50 s | 147.95 s | 148.22 s | 74.95 s | 75.85 s | 77.39 s | 78.43 s | 75.69 s |
| *3* | 111.29 s | 125.09 s | 125.71 s | 45.01 d (138) | 47.09 d | 45.52 d | 47.71 d | 46.50 d |
| *4* | 159.37 s | 150.52 s | 150.88 s | 23.68 d (136) | 24.51 d | 23.51 d | 23.83[a] d | 24.26 d |
| *4a* | | | | 111.54 s | 115.31 s | 114.41 s | 122.63 s | 118.59 s |
| *5* | 111.29 d | 120.63 d | 120.47 d | 152.90[a] s | 154.68 s | 150.62[a] s | 152.15[b] s | 147.41 s |
| *6* | 140.68 s | 136.39 s | 136.67[a] s | 110.39 d (158) | 107.22 d | 107.14[b] s | 112.59[c] s | 115.90 d |
| *7* | 172.56 s | 166.49 s | 166.53 s | 137.83 s | 137.41 s | 135.99 s | 136.80 s | 137.38 s |
| *8* | 51.64 q | 51.97 q | 51.99 q | 111.48 d (159) | 113.79 d | 105.93[b] s | 112.90[c] s | 117.11 d |
| *8a* | | | | 154.29[a] s | 155.90 s | 148.60[a] s | 151.03[b] s | 155.43 s |
| *9* | 23.98 q | 20.10[a] q | 20.03 q | 36.32 t (127) | 36.49 t | 36.15 t | 36.33 t | 36.33 t |
| *10* | 21.92 t | 23.81 t | 24.06 t | 17.05 t (126) | 16.96 t | 17.06 t | 16.96 t | 16.86 t |
| *11* | 121.35 d | 122.32 d | 122.55 d | 34.32 t (126) | 33.98 t | 34.09 t | 33.73 t | 33.99 t |
| *12* | 138.82 s | 135.83 s | 136.04[a] s | 39.17 s | 38.51 s | 39.06 s | 38.96 s | 38.23 s |
| *13* | 39.59 t | 39.38 t | 39.28 t | 57.16 d (133) | 55.74 d | 56.42 d | 55.13 d | 55.61 d |
| *14* | 26.27 t | 26.38 t | 26.26 t | 213.47 s | 209.02 s | 212.36 s | 208.67 s | 207.53 s |
| *15* | 123.71 d | 123.93 d | 124.08 d | 50.67 t (124) | 51.74 t | 50.84 t | 51.60 t | 52.05 t |
| *16* | 131.84 s | 131.34 s | 131.18 s | 23.98 d (130) | 23.63 d | 23.99 d | 23.97[a] d | 23.69 d |
| *17* | 25.52 q | 25.47 q | 25.48 q | 22.52[b] q (125) | 22.71[a] q | 22.51[c] q | 22.50[d] q | 22.58[a] q |
| *18* | 17.55 q | 17.51 q | 17.51 q | 22.71[b] q (125) | 22.52[a] q | 22.70[c] q | 22.61[d] q | 22.52[a] q |
| *19* | 16.08 q | 16.08 q | 16.06 q | 25.58 q (126) | 25.34 q | 25.48 q | 25.98 q | 25.43 q |
| *20* | | 168.48 s | 164.33[b] s | 29.30 q (126) | 28.37 q | 28.64 q | 27.61 q | 28.44 q |
| *21* | | 20.70[a] q | 128.89[c]s | 21.30 q (126) | 21.49 q | 23.80 q | 24.97 q | 21.11 q |
| *22* | | 168.48 s | 130.13 d | | 72.69 t | | 75.12 t | 165.42 s |
| *23* | | 20.42[a] q | 128.48 d | | 195.11 s | | 193.13 s | 129.74 s |
| *24* | | | 133.57[d] d | | 133.38 s | | 133.71 s | 130.17 d |
| *25* | | | 128.48 d | | 130.04 d | | 129.44 d | 128.32 d |
| *26* | | | 130.13 d | | 131.94 d | | 131.81 d | 133.15 d |
| *27* | | | 164.37[b] s | | 128.72 s | | 128.33 s | 128.32 d |
| *28* | | | 128.97[c] s | | 131.94 d | | 131.81 d | 130.17 d |
| *29* | | | 130.13 d | | 130.04 d | | 129.44 d | |
| *30* | | | 128.48 d | | | | | |
| *31* | | | 133.66[d] d | | | | | |
| *32* | | | 128.48 d | | | | | |
| *33* | | | 130.13 d | | | | | |

*Notes*. 1. s – singlet, d – doublet, t – triplet, q – quadruplet. 2. Identical letters (a, b, c, d) denote the values those, to all appearance, should be swapped within one column. 3. For compound **2** we have parenthetically presented $^1J_{C,H}$ values (in Hz).

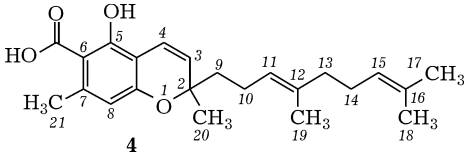
coupled with other spectral data have allowed us to identify this substance as compound **2**. The presence of a tetratomic cycle in the structure under consideration as well as the presence of benzene and cyclohexane rings and of a saturated carbon chain is also confirmed by the values of direct SSCC $^1J_{C,H}$, obtained from the mono-resonance spectrum (see Table 1).

The mass spectrum of substance **2** demonstrates a weak signal of molecular ion $[M^+]$ 342 and an abundant splinter with $m/z$ 175, corresponding to $C_{11}H_{11}O_2$ fragment (see Fig. 1). The spatial arrangement of $C^3H_3$ and $C^4H_3$ protons of the cyclobutane fragment and two methyl groups such as $C^{19}H_3$ and $C^{20}H_3$ has been determined *via* the construction of sub-

stance **2** structure with the help of Draiding models: one can build a molecule without considerable strains only with *cis*-arrangement of the mentioned hydrogen atoms and $CH_3$ groups with respect to each other. The absolute configuration of the chiral centres of compound **2** is not determined yet. We have not found in the literature this compound representing a derivative of cyclobuta[kl]octahydroxanthenol.

Pharmacological experiments demonstrated that substance **2** at a doze of 10 mg/kg introduced to mice *via* intragastric method does not influence the locomotor and emotional activity in the open-field test. In the test with *L*-DOPA characterizing a mediated influence on dopaminergic (adrenergic) system, compound **2** at the same doze exhibited a short-term (during 1 h) enhancing the hypothermic effect of *L*-DOPA, exerting a reliable influence upon this neuromediator system. Methyl ester **1** has not demonstrated any activity in the aforementioned tests. Moreover, compound **2** at a doze of 10 mg/kg exerts a coagulation effect, which is exhibited by a decrease in average prothrombin time of blood clotting.

The content of daurichromenic acid **4** (Fig. 2) in *Rh. adamsii* does not exceed 0.1 %. This compound is obtained by means of chromatographic separation of the benzene extract of plant leaves using the cartridge with an inverse-phase adsorbent. The values of chemical shifts for signals in $^1$H NMR spectrum of the compound isolated are close to those described in the literature [8], whereas the molecular mass of this substance determined by means of an HPLC/MS technique has amounted to 370. The presence of the carboxyl groups is confirmed *via* the methylation of the initial compound by diazomethane resulted, according to HPLC/MS data, in an increase in the molecular mass of the reaction product ($M$ = 384) as well as in the retention time value with respect to the inverse-phase adsorbent.



**4**

Fig. 2. Daurichromenic acid **4**.

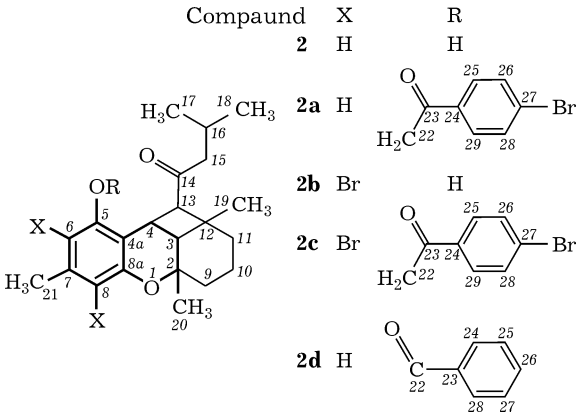
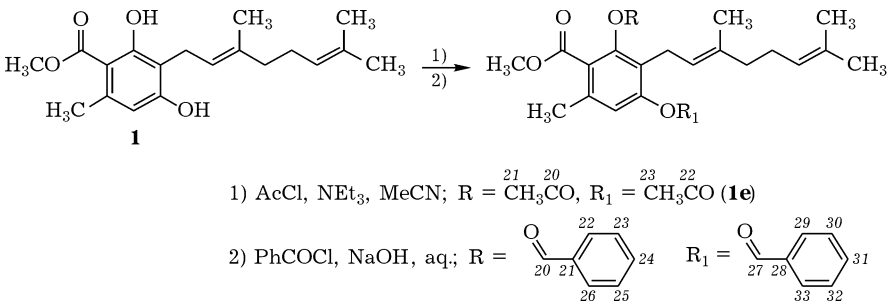



Fig. 3. 1-(3-Methylbutanoyl)-1a,4a,7-trimethyl-1,1a,1a$^1$,2,3,4,4a,9b-octahydrocyclobuta[kl]-xanthene-9-ol **2** and its derivatives **2a–d**. Semiboldface lines designate $C_{11}H_8O_2X_2R$ fragment.

Daurichromenic acid **4** revealed first in *Rhododendron dauricum* [9], exhibits anti-HIV activity ($EC_{50}$ = 0.00567 μg/mL, TI = 3710 [8]).

We have carried out a number of chemical transformations of compounds **1** and **2** isolated. The interaction of xanthenol **2** with *para*-Br-phenacyl bromide in dry acetone medium in the presence of potassium carbonate results in the reaction of the hydroxyl group, thus a corresponding substituted derivative **2a** is formed (Fig. 3). We have observed a complete conversion of initial compound, and the yield of the reaction product after the purification employing a column packed with silica gel amounted to about 75 %. The treatment of compound **2** by dioxane dibromide results in the substitution of both hydrogen atoms in the aromatic ring and the formation of dibromo derivative **2b**. The monitoring of the reaction course by means of HPLC method has demonstrated that a slight heating of the reaction mixture during 2.5–3 h is necessary for the complete conversion of the initial compound. Compound **2b** forms derivative **2c** with the yield amounting to about 65 % due to the interaction with *para*-Br-phenacyl bromide in a similar manner as the initial xanthenol **2**. The reaction of xanthenol **2** with benzoyl chloride in an alkaline medium results in the formation of corresponding benzoic acid ester **2d**. The reaction monitoring by means of HPLC method has demonstrated that the reaction proceeds to a complete extent for 3.5–4 h at a room temperature.




Scheme 1.

Chromato-mass-spectral profiles of derivatives **2a–d** (see Fig. 3) are of an identical appearance: there are a molecular ion $M^+$ with low signal intensity and an abundant shiver corresponding to $C_{11}H_8O_2X_2R$ fragment.

The treatment of methyl ester **1** with bromine solution in $CC1_4$ or with dioxane dibromide, according to HPLC data, results in the formation of a complex mixture of products. To all appearance, it could be caused by the presence of several functional groups in the molecule of compound **1** (two double C=C bonds in the isoprene fragment, hydrogen atom in position $C^5$ labile in electrophilic substitution reactions). Even with the addition of a considerable excess of bromine to the initial compound one can observe that there is no complete bromination of this compound and no formations of single reaction product. We believe that this fact could be caused by the migration of double bonds within the isoprene fragment (which migration especially readily occurs in the acidic medium) and the subsequent bromination of them.

In the present work we have made an attempt to obtain the derivatives of cannabigerorcinic acid methyl ester **1** involving only hydroxyl groups of the aromatic ring. *Via* the interaction of compound **1** with the excess of acetyl chloride and benzoyl chloride, we have obtained derivatives **1d**, **e** (Scheme 1) with the yield of 89 and 31 %, respectively.

All the products obtained from substances **1** and **2**, represent novel compounds.

## EXPERIMENTAL

### *General methods of analysis*

Chromatographic analyzing by HPLC method was carried out employing a Milichrom A-02 chromarograph (EcoNova Co., Novosibirsk); the column being 2 × 75 mm packed with a Prontosi1-120-5-d8 AQ inverse-phases adsorbent with particle diameter of 5 μm, thermostated at 35 °C. An eluent was presented by $CH_3OH$ gradient in 0.1 % trifluoroacetic acid aqueous solution, the flow rate of feeding the eluent amounted to 150 μL/min, the analyzing time being of 30 min. The $^1H$ and $^{13}C$ NMR spectra were registered with the use of spectrometers such as Bruker AV-300 (with operating frequencies of 300.13 MHz for $^1H$ nuclei and of 75.47 MHz for $^{13}C$ nuclei), AM-400 (400.13 MHz ($^1H$) and 100.61 MHz ($^{13}C$)) and DRX-500 (500.13 MHz ($^1H$) and 125.76 MHz ($^{13}C$)) for $CDCl_3$ solutions of substances, using chloroform as an internal standard ($\delta_H$ = = 7.24 ppm, $\delta_C$ = 76.90 ppm). The structure of compounds obtained was established with the help of NMR method basing on the analysis of $^1H$ NMR spectra attracting $^1H–^1H$ double resonance spectra, as well as the analysis of spectra in the mode of *J*-modulation (JMOD), with out-of-resonance and selective suppression of signals from protons, two-dimension spectra of heteronuclear $^{13}C–^1H$ correlation for direct SSCC (C–H COSY, $^1J_{C,H}$ 135 Hz), one-dimension and two-dimension spectra of heteronuclear $^{13}C–^1H$ correlation for long-range spin-spin coupling constants (LRJMD, COLOC, HMBC). High resolution mass spectra were registered using a DFS mass spectrometer (Thermo Scientific) with ionizing electron energy equal to 70 eV. Pharmacological tests were performed according to standard techniques described in [10].

### *Extraction and isolation*

The plant raw material was harvested in 2004 and 2005 nearby the Arshan settlement of the Irkutsk Region and dried to obtain air-

dry condition. The raw material dried was divided into leaves and stems, and then it was grinded to obtain particle size ranging within 0.1–0.5 mm. The grinded plant raw was stored under argon. In order to obtain compounds **1** and **2**, 400 g of the grinded leaves were extracted during 80 h with hexane using a Soxhlet apparatus. The extract obtained was concentrated under vacuum, a residue was suspended in methanol medium and centrifuged then at the rotational frequency equal to 4000 $min^{-1}$ (MLWT-23 centrifuge) within 30 min. The supernatant obtained was evaporated, then a residue obtained was dissolved in 1.5–2.0 mL of $CHCl_3$ by portions of 250–300 mg and chromatographed using a column with packed with silica gel. The column diameter was equal to 13 mm, the mass of $SiO_2$ being 40 g, a hexane – chloroform gradient (100 : 1, 50 : 50, 1 : 100 in volume) being used as the eluent, the volume of fractions amounted to 60 mL. The yield of each substance (**1** and **2**) ranged within 20–25 % with respect to the mass of an extract put into the column. A similar elution pattern was employed also for purifying such products as **1d**, **e** and **2a–d**.

**Methyl ester of (*E*)-3-(3,7-dimethylocta-2,6-dienyl)-2,4-dihydroxy-6-methylbenzoic acid (cannabigerorcinic acid) (1).** The procedure of isolation is described above. The $^1H$ NMR spectrum (δ, ppm; *J*, Hz): 1.57 (brs, 3H, $C^{18}H_3$), 1.65 (brs, 3H, $C^{17}H_3$), 1.78 (brs, 3H, $C^{19}H_3$), 1.98–2.12 (m, 4H, $C^{13}H_2$ and $C^{14}H_2$), 2.43 (s, 3H, $C^9H_3$), 3.41 (d, 2H, $C^{10}H_2$, $J_{10,11}$ = 7.5), 3.90 (s, 3H, $OC^8H_3$), 5.03 (tm, 1H, $C^{15}H$, $J_{15,14}$ = 7, $J_{15,17}$ and $J_{15,18}$ ~ 1.0–1.5), 5.25 (tm, 1H, $C^{11}H$, $J_{11,10}$ = 7.5, $J_{11,13}$ and $J_{11,19}$ ~ 1.0–2.0), 5.90 (s, 1H, $C^4O\underline{H}$), 6.20 (s, 1H, $C^5H$), 12.07 (s, 1H, $C^2O\underline{H}$). Elemental composition: found *m*/*z* 318.1828 $[M]^+$. $C_{19}H_{26}0_4$. Calculated 318.1831.

**Methyl ester of (*E*)-3-(3,7-dimethylocta-2,6-dienyl)-2,4-diacetoxy-6-methylbenzoic acid (1d).** To a solution of 114.6 mg (0.4 mmol) of methyl ester **1** in 10 mL of dry MeCN was dropwise added 85 mg (1.1 mmol) of $CH_3COCl$ dissolved in 3 mL of MeCN, and then 110 mg of $Et_3N$ (1.1 mmol) in 3 mL MeCN was added. The reaction mixture was stirred during 4 h, and then it was poured into 100 mL of water and extracted with diethyl ether (4 × 20 mL). Ethereal extracts obtained were washed with water and dried over $MgSO_4$. After evaporation we have obtained 129.5 mg of substance **1d** with the yield amounting to 89 %. The $^1H$ NMR spectrum (δ, ppm; *J*, Hz): 1.54 (brs, 3H, $C^{18}H_3$), 1.62 (brs, 3H, $C^{17}H_3$), 1.66 (brs, 3H, $C^{19}H_3$), 1.85–2.10 (m, 4H, $C^{13}H_2$ and $C^{14}H_2$); 2.22, 2.24 (both s, for 3H, $C^{21}H_3$, $C^{23}H_3$); 2.34 (s, 3H, $C^9H_3$), 3.11 (d, 2H, $C^{10}H_2$, $J_{10,11}$ = 6.6), 3.83 (s, 3H, $OC^8H_3$), 4.97 (tm, 1H, $C^{11}H$, $J_{11,10}$ = 6.6, $J_{11,13}$ and $J_{11,19}$ < 1.5), 5.02 (tm, 1H, $C^{15}H$, $J_{15,14}$ = 6.4, $J_{15,17}$ and $J_{15,18}$ < 1.5), 6.83 (s, 1H, $C^5H$). Elemental composition: found *m*/*z* 402.2044 $[M]^+$. $C_{23}H_{30}0_6$. Calculated 402.2042.

**Methyl ester of (*E*)-3-(3,7-dimethylocta-2,6-dienyl)-2,4-dibenzoyloxy-6-methylbenzoic acid (1e).** A solution of 113.5 mg (0.4 mmol) of methyl ester **1** in 20 mL of 5 % NaOH aqueous solution was cooled down to 0 °C, then we added dropwise 250 mL (2.16 mmol) of benzoyl chloride and stirred the mixture during 4 h at a room temperature. Further the reaction mixture was extracted with $Et_2O$ (3 × 15 mL), the ethereal extracts obtained were joined together and washed with water to obtain neutral pH of washing waters. The organic phase was dried over $MgSO_4$, the solvent was removed under vacuum. The product obtained was purified *via* chromatographing on silica gel, the product mass after purifying amounted to 59.3 mg (the yield of 31 %). The $^1H$ NMR spectrum (δ, ppm; *J*, Hz): 1.29 (brs, 3H, $C^{19}H_3$), 1.51 (brs, 3H, $C^{18}H_3$), 1.60 (brs, 3H, $C^{17}H_3$), 1.73–1.96 (m, 4H, $C^{13}H_2$ and $C^{14}H_2$), 2.42 (s, 3H, $C^9H_3$), 3.24 (d, 2H, $C^{10}H_2$, $J_{10,11}$ = 6.6), 3.64 (s, 3H, $OC^8H_3$), 4.97 (tm, 1H, $C^{11}H$, $J_{11,10}$ = 6.6, $J_{11,13}$ and $J_{11,19}$ < 1.5), 5.06 (tm, 1H, $C^{15}H$, $J_{15,14}$ = 6.0, $J_{15,17}$ and $J_{15,18}$ < 1.5), 7.02 (s, 1H, $C^5H$), 7.49 (t, 4H, $C^{23}H$, $C^{25}H$, $C^{30}H$, $C^{32}H$, *J* = 7.8), 7.62 (brt, 2H, $C^{24}H$, $C^{31}H$, *J* = 7.8), 8.16 (m, 4H, $C^{22}H$, $C^{26}H$, $C^{29}H$, $C^{33}H$). Elemental composition: found *m*/*z* 526.2348 $[M]^+$. $C_{33}H_{34}O_4$. Calculated 526.2355.

**1-(3-Methylbutanoyl)-1a,4a,7-trimethyl-1,1a,1a$^1$,2,3,4,4a,9b-octahydrocyclobuta[kl]-xanthene-9-ol (2).** The isolation procedure is described above. The $^1H$ NMR spectrum (δ, ppm; *J*, Hz): 0.85 and 0.87 (both d, for 3H, $C^{17}H_3$ and $C^{18}H_3$), $J_{17,16}$ = $J_{18,16}$ = 6.4), 1.09 (s, 3H, $C^{20}H_3$), 1.15 (s, 3H, $C^{19}H_3$), 1.29 (m, 1H,

$C^{11}H^a$), 1.32 (m, 1H, $C^9H^a$), 1.63 (dm, 1H, $C^{10}H^e$, $J_{10e,10a}$ = 13.3), 1.77 (d, 1H, $C^3H$, $J_{3,4}$ = 9.3), 1.82 (ddd, 1H, $C^{11}H^e$, $J_{11e,11a}$ = 13.5, $J_{11e,10a}$ = 4.1, $J_{11e,10e}$ = 2.4), 1.94 (ddddd, 1H, $C^{10}H^a$, $J_{10a,10e}$ = = $J_{10a,9a}$ = $J_{10a,11a}$ = 13.3, $J_{10a,11e}$ = 4.1, $J_{10a,9e}$ = 3.7), 2.05 (ddd, 1H, $C^9H^e$, $J_{9e,9a}$ = 14.2, $J_{9e,10a}$ = 3.7, $J_{9e,10e}$ = 2.2), 2.09 (m, 1H, $C^{16}H$), 2.10–2.18 (m, 2H, $C^{15}H_2$), 2.21 (brs, 3H, $C^{21}H_3$), 2.89 (d, 1H, $C^{13}H$, $J_{13,4}$ = 9.3), 3.79 (dd, 1H, $C^4H$, $J_{4,13}$ = = $J_{4,3}$ = 9.3), 6.28 (brs, 1H, $C^8H$), 6.37 (s, 1H, $C^6H$), 6.78 (s, 1H, $C^5O\underline{H}$). Elemental composition: found $m/z$ 342.2186 $[M]^+$. $C_{22}H_{30}O_3$. Calculated 342.2189.

**9-(2-(4-Bromophenyl)-2-oxoethoxy)-1-(3-methylbutanoyl)-1a,4a,7-trimethyl-1,1a,1a$^1$,2,3,4,4a,9b-octahydrocyclobuta[kl]-xanthene (2a).** A mixture consisting of 55.4 mg (0.16 mmol) of compound **2**, 130 mg (0.94 mmol) of $K_2CO_3$ and 60.9 mg (0.22 mmol) of *para*-bromophenacyl bromide was stirred in 5 mL of dry acetone during 5 h at a room temperature, the course of the reaction was monitored using HPLC technique. Inorganic salts were further filtered, the filtrate obtained was evaporated, a residue (104 mg, yellow-brown oil) was purified chromatographing on silica gel. We have obtained 60.0 mg (the yield being equal to 70 %) of pure product **2a**. The $^1$H NMR spectrum (δ, ppm; *J*, Hz): 0.81 (d, 6H, $C^{17}H_3$ and $C^{18}H_3$, $J_{17,16}$ = $J_{18,16}$ = 6.5), 0.93 (s, 3H, $C^{20}H_3$), 1.10 (s, 3H, $C^{19}H_3$), 1.22 (m, 1H, $C^{11}H^a$), 1.30 (ddd, 1H, $C^9H^a$, $J_{9a,9e}$ = $J_{9a,10a}$ = 13.5, $J_{9a,10e}$ = 3.4), 1.58 (dm, 1H, $C^{10}H^e$, $J_{10e,10a}$ = 13.5), 1.75 (d, 1H, $C^3H$, $J_{3,4}$ = 8.8), 1.79 (dm, 1H, $C^{11}H^e$, $J_{11e,11a}$ = 13.5), 1.99 (m, 1H, $C^{10}H^a$), 2.02 (m, 1H, $C^9H^e$), 2.00–2.19 (m, 3H, $C^{16}H$ and $C^{15}H_2$), 2.20 (s, 3H, $C^{21}H_3$), 3.09 (d, 1H, $C^{13}H$, $J_{13,4}$ = = 9.1), 4.27 (dd, 1H, $C^4H$, $J_{4,13}$ = 9.1, $J_{4,3}$ = 8.8), 5.12 and 5.20 (both d, 1H, $C^{22}H_2$, *J* = 16.2, AB system), 6.22 (brs, 1H, $C^8H$), 6.38 (s, 1H, $C^6H$), 7.60 (d, 2H, $C^{26}H$ and $C^{28}H$, $J_{26,25}$ = $J_{28,29}$ = 8.8), 7.94 (d, 2H, $C^{25}H$ and $C^{29}H$, $J_{25,26}$ = $J_{29,28}$ = 8.8). Elemental composition: found $m/z$ 538.1693 $[M]^+$. $C_{30}H_{35}BrO_4$. Calculated 538.1713.

**6,8-Dibromo-1-(3-methylbutanoyl)-1a,4a,7-trimethyl-1,1a,1a$^1$,2,3,4,4a,9b-octahydrocyclobuta[kl]-xanthene-9-ol (2b).** To a solution of 32 mg (0.09 mmol) of compound **2** in 5 mL of EtOH was added 70 mg (0.28 mmol) dioxane dibromide and then the mixtuire was stirred during 2 h at a room temperature. Further the reaction mixture was added with 100 mg more (0.40 mmol) dioxane dibromide and then it was stirred during 3 h at 60 °C. The reaction mixture was cooled, then it was poured into 50 mL of saturated $NaHCO_3$ solution and extracted with $Et_2O$ (3 × 10 mL). Ethereal extracts were joined together, washed with water and dried over $MgSO_4$. After the solvent removal we have obtained 36.1 mg of compound **2b** (80 % yield). The $^1$H NMR spectrum (δ, ppm; *J*, Hz): 0.84 and 0.86 (both d, for 3H, $C^{17}H_3$ and $C^{18}H_3$, $J_{17,16}$ = $J_{18,16}$ = 6.5), 1.06 (s, 3H, $C^{20}H_3$), 1.15 (s, 3H, $C^{19}H_3$), 1.28 and 1.83 (both m, 2H, $C^{11}H_2$), 1.35 (m, 1H, $C^9H^a$), 1.66 and 1.98 (both m, 2H, $C^{10}H_2$), 1.77 (d, 1H, $C^3H$, $J_{3,4}$ = 9.0), 2.05–2.22 (m, 4H, $C^9H^e$, $C^{16}H$ and $C^{15}H_2$), 2.54 (s, 3H, $C^{21}H_3$), 2.94 (d, 1H, $C^{13}H$, $J_{13,4}$ = 9.0), 3.96 (dd, 1H, $C^4H$, $J_{4,3}$ = $J_{4,13}$ = 9.0), 7.15 (s, 1H, $C^5O\underline{H}$). Elemental composition: found $m/z$ 498.0384 $[M]^+$. $C_{22}H_{28}Br_2O_3$. Calculated 498.0400.

**6,8-Dibromo-1-(3-methylbutanoyl)-9-(2-(4-bromophenyl)-2-oxoethoxy)-1a,4a,7-trimethyl-1,1a,1a$^1$,2,3,4,4a,9b-octahydrocyclobuta[kl]-xanthene (2c).** A mixture consisting of 20.1 mg (0.04 mmol) of dibromo derivative **2b**, 17 mg (0.06 mmol) of *para*-bromophenacyl bromide and 50 mg of $K_2CO_3$ in 10 mL of dry acetone was stirred during 4 h. Then a precipitate was filtered and the solvent was evaporated. The product was purified *via* chromatographing on $SiO_2$. We have obtained 18.1 mg (65 % yield) of compound **2c**. $^1$H NMR spectrum (δ, ppm; *J*, Hz): 0.78 and 0.79 (both d, for 3H, $C^{17}H_3$ and $C^{18}H_3$), $J_{17,16}$ = $J_{18,16}$ = 6.5), 0.89 (s, 3H, $C^{20}H_3$), 1.02 (s, 3H, $C^{19}H_3$), 1.26 and 1.79 (both m, 2H, $C^{11}H_2$), 1.35 and 2.19 (both m 2H, $C^9H_2$), 1.66 (m, 1H, $C^{10}H^e$), 1.75 (d, 1H, $C^3H$, $J_{3,4}$ = 9.0), 1.87–2.14 (m, 4H, $C^{10}H^a$, $C^{16}H$, $C^{15}H_2$), 2.56 (s, 3H, $C^{21}H_3$), 3.24 (d, 1H, $C^{13}H$, $J_{13,4}$ = 9.0), 4.34 (d.d, 1H, $C^4H$, $J_{4,13}$ = $J_{4,3}$ = 9.0), 5.14 and 5.52 (both d, for 1H, $C^{22}H_2$, *J* = 16.2, AB system), 7.60 (d, 2H, $C^{25}H$, $C^{29}H$, $J_{25,26}$ = $J_{29,28}$ = 8.6), 7.87 (d, 2H, $C^{26}H$, $C^{28}H$, $J_{26,25}$ = $J_{28,29}$ = 8.6). Elemental composition: found $m/z$ 693.9870 $[M]^+$. $C_{30}H_{33}Br_3O_4$. Calculated 693.8824.

**1a,4a,7-Trimethyl-1-(3-methylbutanoyl)-1,1a,1a$^1$,2,3,4,4a,9b-octahydrocyclobuta[kl]-xanthene-9-yl benzoate (2d).** A solution of 82.1 mg (0.24 mmol) of compound **2** in 10 mL of

5 % aqueous NaOH was cooled down to 0 °C, then 169 mg (1.21 mmol) of benzoyl chloride was added and the mixture was stirred during 4 h. Further the reaction mixture was diluted with 10 mL of water and then extracted with $Et_2O$ (3 × 15 mL), ethereal extracts were joined together and washed with water to obtain neutral pH of washing waters. The organic phase was dried over $MgSO_4$ and evaporated. The product obtained was purified by means of chromatographing on silica gel. As a result, we have obtained 64.2 mg of compound **2d** (60 % yield). The $^1$H NMR spectrum (δ, ppm; *J*, Hz): 0.80 and 0.82 (both d, for 3H, $C^{17}H_3$ and $C^{18}H_3$, $J_{17,16} = J_{18,16} = 6.5$), 0.99 (s, 3H, $C^{19}H_3$), 1.03 (s, 3H, $C^{20}H_3$), 1.22 (m, 1H, $C^{11}H^a$), 1.31 (m, 1H, $C^9H^a$), 1.59 (dm, 1H, $C^{10}H^e$, $J_{10e,10a} = 13.5$), 1.76 (dm, 1H, $C^{11}H^e$, $J_{11e,11a} = 13.5$), 1.78 (d, 1H, $C^3H$, $J_{3,4} = 9.0$), 1.93–2.18 (m, 4H, $C^{10}H^a$, $C^{15}H_2$ and $C^{16}H$), 2.05 (dm, $C^9H^e$, $J_{9e,9a} = 13.5$), 2.28 (brs, 3H, $C^{21}H_3$), 3.12 (d, 1H, $C^{13}H$, $J_{13,4} = 9.0$), 4.04 (dd, 1H, $C^4H$, $J_{4,3} = J_{4,13} = 9.0$), 6.59 (brs, 1H, $C^6H$), 6.64 (brs, 1H, $C^8H$), 7.52 (t, 2H, $C^{25}H$, $C^{27}H$, $J = 7.5$), 7.61 (tt, 1H, $C^{26}H$, $J_{26,25} = 7.5$, $J_{26,24} = 1.2$), 8.28 (dd, 2H, $C^{24}H$, $C^{28}H$, $J_{24,25} = J_{28,27} = 7.5$, $J_{24,26} = J_{28,26} = 1.2$). Elemental composition: found *m*/*z* 446.2447 $[M]^+$. $C_{29}H_{34}O_4$. Calculated 446.2452.

**Daurichromenic acid (4).** Air-dry leaves 3.55 g in mass were extracted with benzene using a Soxhlet apparatus during 15 h. The extract obtained was evaporated, put onto the inverse-phase adsorbent and eluted then successively with 50, 70, 90 % aqueous solution of methanol, and then with pure methanol. A washout resulted from 100 % methanol was evaporated to obtain 0.21 g of a residue which was chromatographed using a column packed with silica gel (Merck, 60–200 μm; the column being of 10 mm in diameter, 31 cm long). The elution was performed first of all using chloroform, and then using a stepwise ethanol gradient in chloroform increasing the ethanol concentration from 2 up to 100 %. The volume of each step amounted to 40 mL; we collected fractions of 15–20 mL in volume. The fraction No. 2 contained 3 mg of substance **4**. The $^1$H NMR spectrum (δ, ppm; *J*, Hz): 1.38 (s, 3H, $C^{20}H_3$), 1.55 (brs, 3H, $C^{19}H_3$), 1.57 (brs, 3H, $C^{18}H_3$), 1.65 (m, 3H, $C^{17}H_3$), 1.60–1.80 (m, 2H, $C^9H_2$), 1.87–2.13 (m, 6H, $C^{10}H_2$, $C^{13}H_2$, $C^{14}H_2$), 2.50 (s, 3H, $C^{21}H_3$), 5.03 (tm, 1H, $C^{15}H$, $J_{15,14} = 7.0$), 5.06 (tm, 1H, $C^{11}H$, $J_{11,10} = 7.5$), 5.42 (d, 1H, $C^3H$, $J_{3,4} = 10.1$), 6.16 (s, 1H, $C^8H$), 6.69 (d, 1H, $C^4H$, $J_{4,3} = 10.1$). The values chemical shifts presented for signals in the NMR spectrum are close to those described in the literature [8]. $M^+$ (HPLC/MS) = 370; $M^+$ (Me ester, HPLC/MS) = 384.

## CONCLUSION

Three compounds belonging to the class of prenylated phenols have been for the first time isolated from *Rhododendron adamsii*: daurichromenic acid, methyl ester of cannabigerorcinic acid and 1-(3-methylbutanoyl)-1a,4a,7-trimethyl-1,1a,1a$^1$,2,3,4,4a,9b-octahydrocyclobuta[kl] xanthene-9-ol; the latter we have not found in the literature. We have for the first time revealed in a naturally occurring object (*Rhododendron adamsii)* a derivative of cannabigerorcinic acid such as methyl ester **1.** We have performed bromination, benzoylation and acylation of cannabigerorcinic acid methyl ester, as well as bromination, benzoylation and phenacylation of 1-(3-methylbutanoyl)-1a,4a,7-trimethyl-1,1a,1a$^1$,2,3,4,4a,9b-octahydrocyclobuta[kl]-xanthene-9-ol resulted in obtaining six novel compounds. It has been revealed that the isolated cyclobutaoctahydroxanthenol exhibits hypothermic and clotting activities.

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