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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and analgesic activity of stereoisomers of 2-(3(4)-hydroxy-4(3)-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diols

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Abstract 2-(3(4)-Hydroxy-4(3)-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diols were found recently to possess high analgesic activity and low acute toxicity. Stereoisomers of these compounds with high optical purity were synthesized from (+)- and (−)-α-pinenes for the first time in this work. The structure of (4*S*)-**4b** isomer was confirmed by the XRD data. Studies of analgesic activity of the resulting products demonstrated that neither the absolute configuration nor *cis*- or *trans*-arrangement of vicinal oxygen atoms plays a significant role in manifestation of analgesic effect by these isomers, while only (4*S*)-**4b** isomer, but not (4*R*)-**4b** demonstrated the analgesic effect.

Keywords Terpene · Chromene · Heterocyclic compounds · Analgesic activity · Acetic acid-induced writhing test · Hot plate test · Stereoisomers

Introduction

It is known that reactions of monoterpenoids of the pinane, *para*-menthane, and carane series with aldehydes can give rise to heterocyclic compounds of various structural types (Mikhalchenko *et al.*, 2013b; Baishya *et al.*, 2013; Il'ina *et al.*, 2011; Saha *et al.*, 2010; Il'ina *et al.*, 2007, 2010; Salakhutdinov *et al.*, 1998). Products of these reactions are of interest as many of them exhibit a significant analgesic activity (Mikhalchenko *et al.*, 2013a; Kurbakova *et al.*, 2014; Il'ina *et al.*, 2014). Chromenes **4a,b** (Scheme 1) turned out to be among the most promising compounds in this regard (Il'ina *et al.*, 2014); these compounds are produced by interaction between (−)-*cis*-verbenol epoxide (**1**) or monoterpenoid (1*R*,2*R*,6*S*)-**2** with vanillin (**3a**) or isovanillin (**3b**) in the presence of montmorillonite clay. Compounds **4a,b** are formed as a mixture of diastereomers with respect to position 4 (at the carbon atom bonded to the methyl and hydroxyl groups) at a ~3:1 ratio, with (*S*)-isomer being predominant. Their analgesic activity was studied without isomer separation. Furthermore, commercially available verbenone ((−)-**5**) with enantiomeric excess (*ee*) of 70 % was used to synthesize compounds (−)-**1** and (1*R*,2*R*,6*S*)-**2** (Il'ina *et al.*, 2014), which ensured an identical enantiomeric purity of the conversion products. Meanwhile, it is known that the absolute configuration and isomeric composition often have a crucial effect on biological activity of compounds, which was earlier demonstrated when studying the antiparkinsonian activity of diol **2** (Ardashov *et al.*, 2011). This investigation was aimed at producing stereoisomers of compounds **4a,b** and studying their analgesic activity.

Chemistry

The first important task was to synthesize enantiomerically pure compounds **4a,b**, their optically pure antipodes, and analogs with *cis*-position of oxygen-containing substituents in cyclohexane ring. When performing these studies, we relied upon the previously elaborated approaches to producing isomeric *cis*- and *trans*-verbenol epoxides from (+)- and (−)-α-pinenes ((+)- and (−)-**6**) (Ardashov *et al.*,

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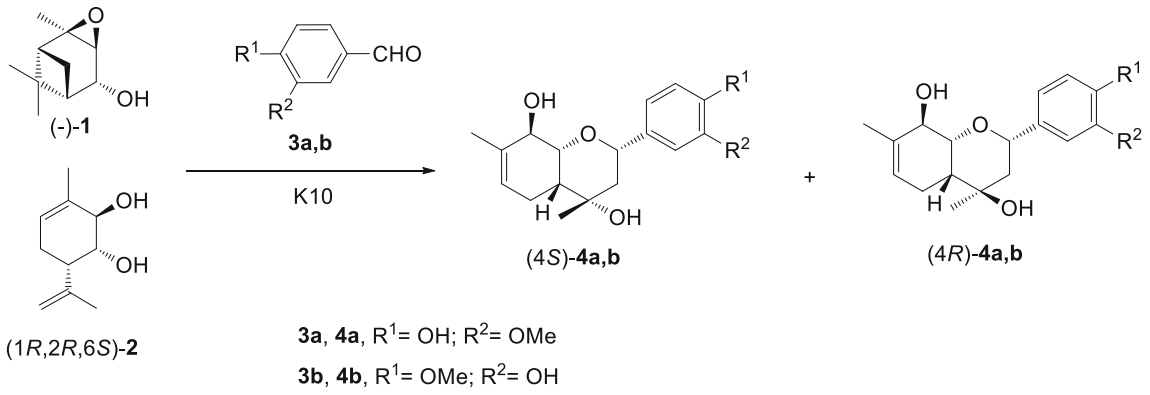


Scheme 1 Interaction of compounds **1** and **2** with aldehydes **3a,b**

2011), where it has been demonstrated that enantiomeric excess is not reduced during these transformations.

To produce (+)-enantiomers of *cis*- and *trans*-verbenol epoxides, we oxidized (+)-α-pinene ((+)-**6**) by lead tetraacetate at the first stage, which gave rise to a mixture of acetates (+)-**7** and (+)-**8** (Scheme 2). A portion of the resulting mixture underwent isomerization in acetic acid (Scheme 2, way **A**) followed by saponification, which gave rise to a mixture of *cis*- and *trans*-verbenols at a 1:10 ratio; individual (+)-*trans*-verbenol ((+)-**9**) was isolated from this mixture by column chromatography. (+)-*trans*-Verbenol epoxide ((+)-**10**) was synthesized by epoxidation of compound (+)-**9** using *t*-BuOOH and $VO(acac)_2$. In order to produce (+)-*cis*-verbenol epoxide ((+)-**1**), the remaining portion of the mixture of acetates (+)-**7** and (+)-**8** was subjected to saponification followed by oxidation to (+)-verbenone ((+)-**5**) (Scheme 2, way **B**). (+)-*cis*-Verbenol epoxide ((+)-**1**) was produced by epoxidation of compound (+)-**5** with H_2O_2 followed by reduction. The yields of compounds (+)-**1** and (+)-**10** calculated based on (+)-α-pinene ((+)-**6**) were 6 and 14 %, respectively.

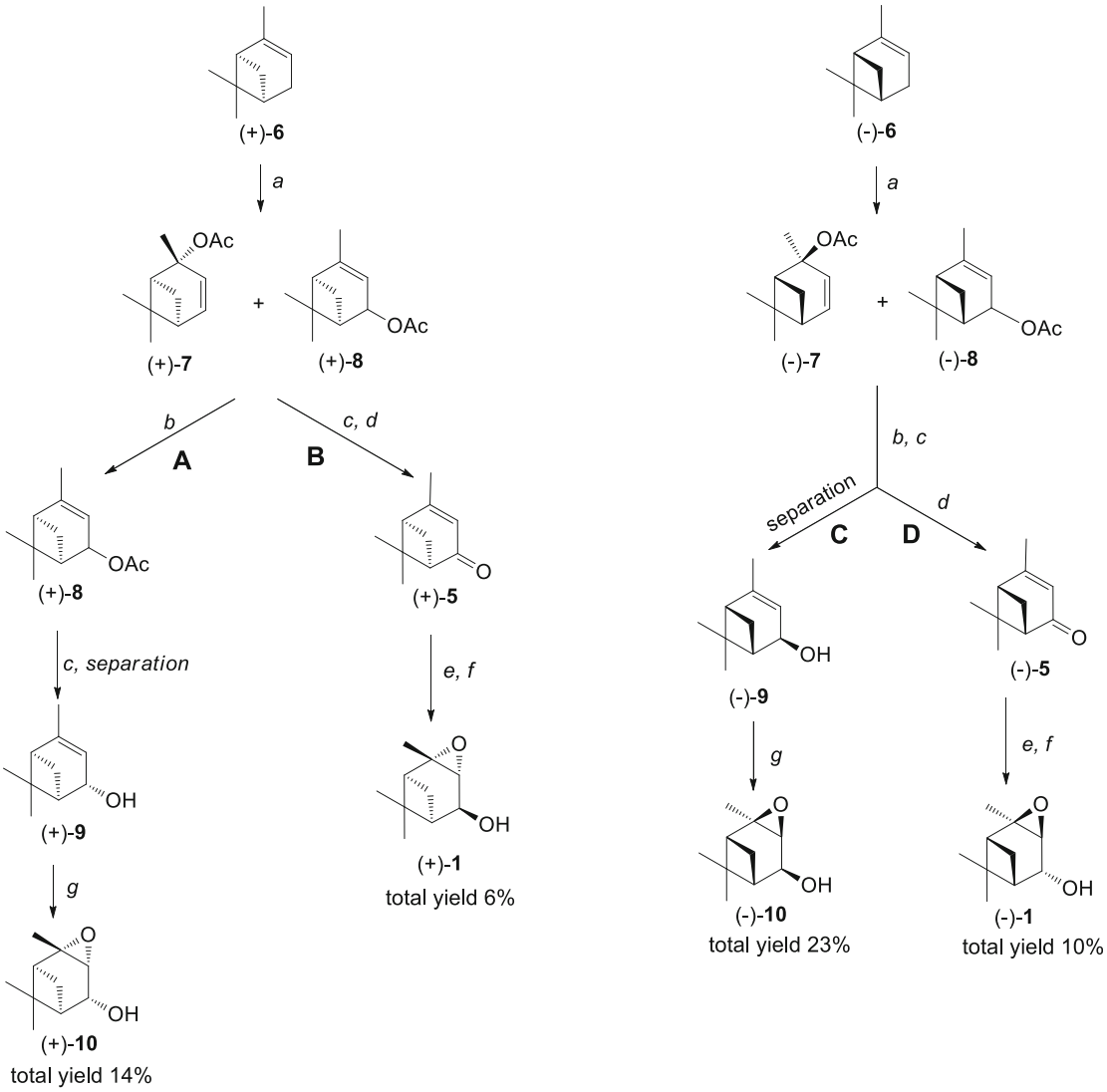
(−)-Enantiomers of *cis*- and *trans*-verbenol epoxides ((−)-**1** and (−)-**10**) were synthesized according to the same scheme; however, the entire mixture of acetates (−)-**7** and (−)-**8** that had been produced by oxidation of (−)-α-pinene ((−)-**6**) was subjected to isomerization and saponification (Scheme 2). A portion of the resulting mixture of isomeric verbenols was used to isolate individual (−)-*trans*-verbenol ((−)-**9**) (Scheme 2, way **C**). The mixture fractions of verbenols obtained during column chromatography were combined with the second portion of the initial mixture. The resulting mixture was oxidized with $Na_2Cr_2O_7$ to (−)-verbenone ((−)-**5**) (Scheme 2, way **D**). The synthesized compounds (−)-**5** and (−)-**9** were further converted to the target epoxides (−)-**1** and (−)-**10**, respectively. This modification of the procedure made it possible to optimize synthesis and increase the yield of the target products (−)-**1** and (−)-**10** calculated based on α-pinene ((−)-**6**), to 10 and 23 %, respectively.

The interaction of (−)- and (+)-*cis*-verbenol epoxides ((−)- and (+)-**1**) with aldehydes **3a,b** in the presence of montmorillonite K10 clay gave rise to the target chromenes **4a,b** and **11a,b**; furthermore, the isomerization products diol (+)-**2**, keto alcohol **12**, and hydroxyacetaldehyde **13** were isolated from the reaction mixture (Scheme 3). It should be mentioned that compound **13** is labile under conditions of column chromatography; hence, sometimes it cannot be isolated from the reaction mixture. The yields of compounds **4a** and **4b** obtained via the reaction of (−)-**1** with vanillin (**3a**) and isovanillin (**3b**) were 26 and 15 %, respectively; those for (+)-enantiomers **11a** and **11b** were 15 and 17 %. The moderate yields of the target products are caused by significant lability of verbenol epoxides in acidic environment; as a result, the reaction mainly proceeds via the isomerization route and is accompanied by resinification processes.

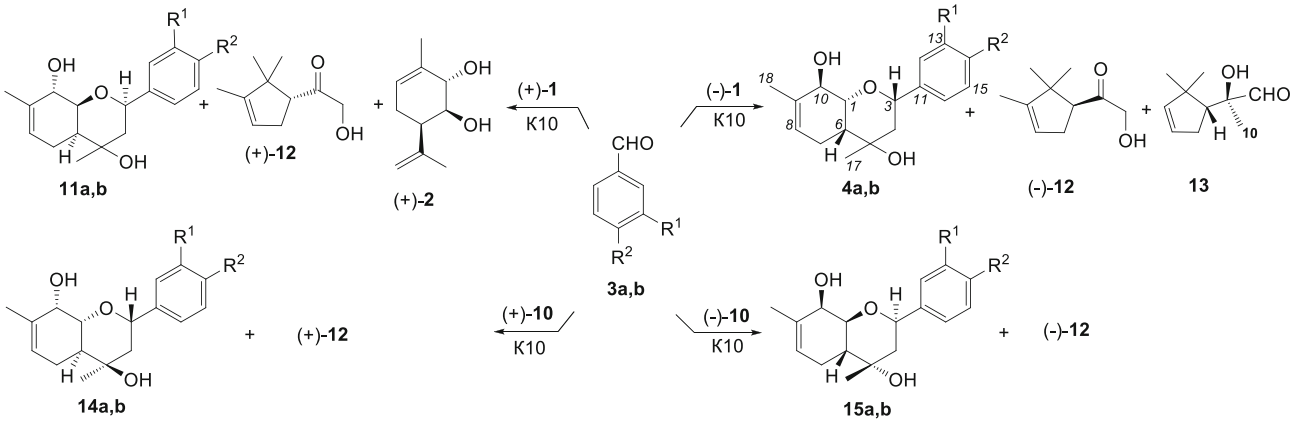
In a similar way, the interaction of (+)- and (−)-*trans*-verbenol epoxides ((+)- and (−)-**10**) with aldehydes **3a** and **3b** yielded isomeric chromenes **14a**,**b** and **15a**,**b**. The yield of compound **14a** in the reaction between (+)-*trans*-verbenol epoxide ((+)-**10**) and vanillin (**3a**) was 18 %, while that of compound **14b** (in the reaction with isovanillin (**3b**)) was 9 %. The interaction of (−)-*trans*-verbenol epoxide ((−)-**10**) with aldehydes **3a** and **3b** gave rise to products **15a** and **15b** with the yield of 15 and 8 %. It should be noted that the compounds **14a**,**b** and **15a**,**b** were isolated as individual diastereomers ((*S*)-isomers in the case of compounds **15a**,**b** and (*R*)-isomers in the case of compounds **14a**,**b**).

Thus, isomeric 2-(3(4)-hydroxy-4(3)-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diols **4a**,**b**, **11a**,**b**, **14a**,**b**, and **15a**,**b** with high optical purity were synthesized for the first time.

The diastereomers (4*R*)- and (*4S*)-**4a**, as well as (4*R*)- and (*4S*)-**4b**, were separated by preparative HPLC. It was



Scheme 2 Synthesis of stereoisomeric verbenol epoxides: (*a*) $Pb(OAc)_4$; (*b*) CH_3CO_2H; (*c*) KOH/MeOH/H_2O; (*d*) $Na_2Cr_2O_7$; (*e*) H_2O_2/NaOH; (*f*) $LiAlH_4$; (*g*) *t*-BuOOH/VO(acac)$_2$



3a, **4a**, **12a**, **14a**, **15a**, R^1= OMe; R^2= OH
3b, **4b**, **12b**, **14b**, **15b**, R^1= OH; R^2= OMe

Scheme 3 Synthesis of isomeric chromenes

found that (4*S*)-isomers of both substances are characterized by shorter retention time under conditions of gradient elution than (4*R*)-isomers, which made it possible to isolate both pairs of diastereomers of **4a** and **4b** as individual compounds.

The structure of isomer (4*S*)-**4b** was additionally verified by the XRD data (Fig. 1). The conformation of the carbocycle is close to the distorted envelope conformation with C1 and C6 atoms deviation by +0.502(2) and −0.184(2) Å from the rest atoms plane. A similar conformation is also observed in Abiespiroside A (Yang *et al.*, 2010). The heterocycle has a chair conformation with equatorial hydroxyphenyl. Hydroxyphenyl orientation is characterized by the dihedral angle HC3C11C12 4°. Let us mention the intramolecular hydrogen bond O4–H···O5 (H···O distance, 2.30(3) Å; O–H···O angle, 109(2)°). Hydroxyl O4H and the remaining OH groups form intermolecular hydrogen bonds (distances H···O 2.00(3)–2.17(3) Å, O–H···O 149(2)–157(2)°), resulting in layer formation (2D architecture of the crystal).

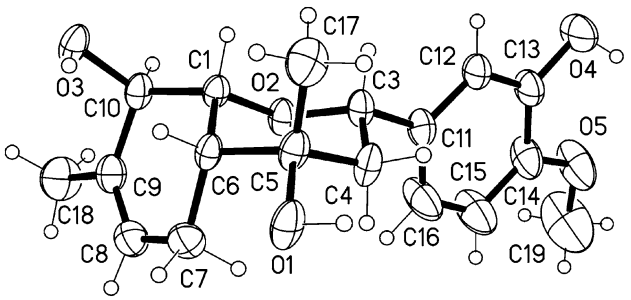


Fig. 1 Molecular structure of compound (4*S*)-**4b** (the thermal ellipsoids are drawn at the 50 % probability level)

Biology

The analgesic activity of the resulting heterocyclic compounds was studied using the acetic acid writhing test (0.75 % acetic acid, 0.1 ml per animal) (Koster *et al.*, 1959) at a dose of 10 mg/kg. The dose of 10 mg/kg was chosen based on previously obtained data for analgesic activity of this type of compounds (Il'ina *et al.*, 2014). Diclofenac sodium was used at the same dose as a reference drug. The results are listed in Table 1.

The studies of analgesic activity were started using compound **4a**, which is a vanillin derivative and consists of a mixture of (*S*)- and (*R*)-isomers with respect to position 4 at a 3:1 ratio. It is clear from the data listed in Table 1 (No. 1–3) that both diastereomers (4*S*)-**4a** and (4*R*)-**4a** contributed to the analgesic effect, although the (4*S*)-**4a** isomer exhibited greater effectiveness. Isomeric compounds **11a**, **14a**, and **15a** exhibited a significant analgesic activity comparable to that of the reference drug, diclofenac sodium.

Isovanillin derivative **4b** (3:1) exhibited its analgesic effect due to the major isomer (4*S*)-**4b**, which showed a reliable analgesic activity, while diastereomer (4*R*)-**4b** had no significant effect on the total number of acetic acid-induced writhes in animals. Similar to vanillin derivatives, isomers **11b**, **14b**, and **15b** showed a significant analgesic activity.

Table 1 Analgesic activity of compounds **4a,b**, **11a,b**, **14a,b**, **15a,b**, and sodium diclofenac (10 mg/kg dose)

No.	Compound	Acetic acid-induced writhing test, number of writhes		Pain inhibition (%)[a]
		Control	Mean ± SD	
1	**4a**	13.8 ± 0.8	8.0 ± 1.3**	42
2	(4*S*)-**4a**		6.3 ± 1.6***	54
3	(4*R*)-**4a**		9.6 ± 1.5**	30
4	**11a**		6.3 ± 1.4***	54
5	**14a**		8.0 ± 1.4**	42
6	**15a**		6.4 ± 1.6**	54
7	**4b**	12.0 ± 0.6	9.3 ± 0.9*	23
8	(4*S*)-**4b**		8.0 ± 1.3*	33
9	(4*R*)-**4b**		10.4 ± 1.6	13
10	**11b**		7.6 ± 1.6*	37
11	**14b**		7.5 ± 0.8**	38
12	**15b**		8.8 ± 1.4*	27
13	Diclofenac sodium	10.1 ± 1.9	5.0 ± 1.1***	50

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ in comparison with control

[a] % of pain inhibition = $(t_{control} - t_{exp})/t_{control} \times 100$ %

Conclusion

Thus, we have synthesized isomeric 2-(3(4)-hydroxy-4(3)-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diols characterized by high optical purity from (+)- and (−)-α-pinenes for the first time. Individual (4*S*)- and (4*R*)-diastereomers of compounds **4a,b** have been isolated. The structure of compound (4*S*)-**4b** has been confirmed by the XRD data. Studies of the analgesic activity of the resulting products have demonstrated that in general neither the absolute configuration nor *cis*- or *trans*-position of vicinal oxygen atoms plays a significant role in manifestation of the analgesic effect by the resulting isomers, while only (4*S*)-**4b** isomer, but not (4*R*)-**4b** demonstrated the analgesic effect.

Experimental

Chemistry

α-Pinenes of high optical purity: (+)-α-pinene "Sigma-Aldrich" ($[\alpha]_D^{20}$ +50.5, 98 % *ee*) and (−)-α-pinene "Fluka" ($[\alpha]_D^{20}$ −48.4, 93 % *ee*) were used as starting compounds for the synthesis. All chemicals reagents used in this work were of commercial grade, and their purity was not less 98 %. As catalyst, we used K10 clay "Aldrich." The clay was calcinated at 105 °C for 3 h immediately before use. CH_2Cl_2 was passed through calcinated Al_2O_3. Silica gel (SiO_2; Macherey–Nagel; 60–200 μ) was used for column chromatography. Fractions obtained after column chromatography were analyzed using gas chromatograph Agilent 7820A with flame ionization detector and HP-5 capillary column (0.25 mm ∅ × 30 m × 0.25 μm); He as carrier gas was used (flow rate 2 ml/min, flow division 99:1).

HPLC analyses were performed on Agilent 1200 Series chromatograph in gradient elution mode using water/MeOH system as a mobile phase. Column: Agilent Prep-C18 Scalar, ∅4.6 × 150 mm, diameter of particles 10 μm. Gradient: 0 min—5 % MeOH, 10 min—70 % MeOH, 15 min—70 % MeOH, 16 min—100 % MeOH, 20 min—100 % MeOH; flow rate 1 ml/min. Large-scale separations were carried out on the same chromatograph using preparative column (Grace Davison Discovery Science, ∅2.5 × 30 cm, packed with Agilent Prep-C18 sorbent with the diameter of particles 10 μm). Gradient: 0 min—5 % MeOH, 24 min—70 % MeOH, 36 min—70 % MeOH, 39 min—100 % MeOH, 45 min—100 % MeOH; flow rate 25 ml/min.

^{1}H and ^{13}C NMR: *Bruker DRX-500* apparatus at 500.13 MHz (^{1}H) and 125.76 MHz (^{13}C), *J* in Hz; and *Bruker AV-300* apparatus at 300.13 MHz (^{1}H) and 75.48 MHz (^{13}C), *J* in Hz; chemical shifts δ in ppm rel. to residual $CHCl_3$ (δ(H) 7.24, δ(C) 76.90 ppm). Structures were elucidated by analyzing the ^{1}H NMR spectra, including ^{1}H–^{1}H double resonance spectra and ^{1}H–^{1}H 2D homonuclear correlation, *J*-modulated ^{13}C NMR spectra (JMOD), and ^{13}C–^{1}H 2D heteronuclear correlation with one-bond and long-range spin–spin coupling constants (C–H COSY, ^1J(C,H) = 160 Hz, COLOC, $^{2,3}J$(C,H) = 10 Hz). Atom numeration used in NMR spectra description is shown in Scheme 3.

HR-MS: *DFS-Thermo-Scientific* spectrometer in a full scan mode (15–500 *m/z*, 70 eV electron-impact ionization, direct sample injection).

Spectral and analytical investigations were carried out at Collective Chemical Service Center of Siberian Branch of the Russian Academy of Sciences.

The X-ray diffraction data of (4S)-**4b** compound were collected on a Bruker Kappa Apex II CCD diffractometer (graphite monochromator, Mo Kα (λ = 0.71073 Å) radiation, temperature 296 K, φ,ω-scans). Absorption corrections were applied using the empirical multi-scan method with the SADABS program. The structure was solved by direct method using SHELXS program and refined in anisotropic approximation for non-hydrogen atoms using the SHELXL program. The hydrogen atoms at the carbon atoms were refined with a riding model. The hydroxyl hydrogen atoms were located from different Fourier maps and refined in isotropic approximation. Crystallographic data: monoclinic system, space group $P2_1$, a = 7.0095(2), b = 8.0462(3), c = 15.3602(6) Å, β = 94.093(2)°, V = 864.10(5) Å^3, $C_{18}H_{24}O_5$, Z = 2, d = 1.231 g/cm^3, μ = 0.089 mm^{-1}. A total of 16,259 reflections with $\theta < 28.3°$ were collected; 4249 unique and 4093 observed reflections ($I > 2\sigma$). Refinement parameters: R = 0.0418, wR_2 = 0.1098 for observed and R = 0.0437, wR_2 = 0.1141 for all reflections, S = 1.049, absolute structure parameter −0.2(9). The X-ray diffraction data have been deposited at the Cambridge Crystallographic Data Center as CCDC 1047705. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi or deposit@ccdc.cam.ac.uk.

1. Synthesis of (+)-*cis*-verbenol epoxide ((+)-1) and (+)-*trans*-verbenol epoxide ((+)-10).

(+)-α-Pinene (+)-**6** (*ee* 98 %, 12.5 g) was dissolved in dry benzene (200 ml) and warmed to 65–68 °C. $Pb(OAc)_4$ (39 g) was added for 9 min to the solution, then the mixture was stirred for 1 h at 65–68 °C, the solution was cooled to r.t., and precipitate was filtered off. Water (150 ml) was added to the filtrate for the precipitation of lead oxide. The mixture was swirled vigorously every 10 min for 1 h. The precipitate was filtered off, and the layers of the filtrate were separated. The aqueous phase was

extracted with Et_2O (3 × 75 ml). Organic extracts were combined, dried over $MgSO_4$, then filtered, and concentrated by rotary evaporation to give mixture (13 g) of acetates (+)-**7** and (+)-**8** containing benzene as an impurity.

Half of the obtained mixture (6.5 g) was dissolved in MeOH (9 ml). The solution of KOH (4.3 g) in the mixture of MeOH (25 ml) and H_2O (4 ml) was added. After 24 h of stirring at ambient temperature, the reaction mixture was diluted with H_2O (50 ml) and extracted with Et_2O (4 × 40 ml). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give a mixture of (+)-*cis*-verbenol and (+)-*trans*-verbenol ((+)-**9**) (6.0 g).

The mixture of verbenols (6.0 g) was dissolved in Et_2O (75 ml) and cooled to 0 °C. The mixture of $Na_2Cr_2O_7 \times 2H_2O$ (6.9 g), H_2O (25 ml), and H_2SO_4 (2.6 ml, $d = 1.86$) was added to this solution for 10 min. The reaction mixture was stirred for 1 h at 0 °C and then 24 h at r.t. Then, H_2O (50 ml) was added, the layers were separated, and the aqueous phase was extracted with Et_2O (3 × 50 ml). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (50 ml) and brine (50 ml), dried over $MgSO_4$, filtered, and concentrated. The residue was separated on a SiO_2 (17 g) column, with gradient of Et_2O in hexane from 2 to 100 % as eluent, to obtain 1.42 g of (+)-verbenone ((+)-**5**) (20 % yield based on the starting (+)-α-pinene ((+)-**6**)).

(+)-Verbenone ((+)-**5**) (1.42 g) was dissolved in MeOH (15 ml) and cooled to 10 °C. 35 % H_2O_2 (3 ml) followed by 6 N NaOH (1 ml) was added, and the mixture was stirred for 2.5 h at 8–11 °C, diluted with H_2O (30 ml), and extracted with EtOAc (4 × 25 ml). Combined organic layers were washed with H_2O (2 × 35 ml), dried over $MgSO_4$, filtrated, and concentrated to give (+)-verbenone epoxide as an intermediate product (0.97 g, 65 %, not shown in Scheme 2).

A solution (+)-verbenone epoxide (0.97 g) in Et_2O (10 ml) was added to a suspension of $LiAlH_4$ (0.230 g) in Et_2O at 0 °C for 10 min with stirring. The mixture was stirred for 2.5 h at 0 °C, and then H_2O (1.5 ml) was slowly added. The precipitate was filtered, and filtrate was washed with H_2O (3 × 20 ml) and dried over Na_2CO_3. The solvent was distilled off, and (+)-*cis*-verbenol epoxide ((+)-**1**) (0.470 g, 48 %) was obtained. The ^1H and ^{13}C NMR spectral data of (+)-**1** coincided with those reported in the literature (Ardashov *et al.*, 2011).

The second part (6 g) of the mixture of acetates (+)-**7** and (+)-**8** obtained at the first stage was dissolved in acetic acid (25 ml) and stirred for 1 h at r.t. The reaction mixture was diluted with H_2O (30 ml) and extracted with Et_2O (4 × 15 ml). The combined organic extracts were washed with saturated $NaHCO_3$ (8 × 25 ml), dried over Na_2SO_4, filtered, and concentrated to obtain (+)-**8** (5 g, 83 %).

Then, (+)-**8** (5 g) was dissolved in MeOH (7 ml). The solution of KOH (2.7 g) in MeOH (11.5 ml) and H_2O (2.5 ml) was added. After 24 h of stirring, the reaction mixture was diluted with H_2O (20 ml) and extracted with EtOAc (5 × 15 ml). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to give a mixture of verbenols (6.0 g). The mixture was separated on a SiO_2 (100 g) column using gradient of Et_2O in hexane from 0 % to 100 % as eluent to obtain 1.62 g of (+)-*trans*-verbenol ((+)-**9**) (42 %).

(+)-*trans*-Verbenol ((+)-**9**) (1.62 g) was dissolved in dry toluene (100 ml), and then $VO(acac)_2$ (0.003 g) and 5.5 M solution of *t*-BuOOH in hexane (2.3 ml) were added. The reaction mixture was refluxed for 40 min. The solution was cooled to r.t. and washed with saturated Na_2SO_3 (100 ml) and H_2O (2 × 100 ml). Then, reaction mixture was dried over Na_2CO_3, filtered, and concentrated to give (+)-*trans*-verbenol epoxide ((+)-**10**) (1.11 g, 62 %). The ^1H and ^{13}C NMR spectral data of (+)-**10** coincided with those reported in the literature (Ardashov *et al.*, 2011).

2. Synthesis of (−)-*cis*-verbenol epoxide ((−)-1) and (−)-*trans*-verbenol epoxide ((−)-10).

Similar to the synthesis of acetates (+)-**7** and (+)-**8**, a mixture of (−)-**7** and (−)-**8** (30 g) containing benzene as impurity was obtained from (−)-α-pinene ((−)-**6**) (25 g, *ee* 93 %).

Then, the entire mixture of (−)-**7** and (−)-**8** (30 g) was subjected to isomerization in acetic acid in accordance with the procedure of preparation (+)-**8** (see above) to give acetate (−)-**8**.

The obtained acetate (−)-**8** was dissolved in MeOH and subjected to saponification (see procedure of saponification (+)-**8** to (+)-**9**) to get a mixture of (−)-*cis*-verbenol and (−)-*trans*-verbenol ((−)-**9**) (15.8 g).

The part of the mixture of (−)-*cis*-verbenol and (−)-*trans*-verbenol ((−)-**9**) (7.9 g) was separated on a SiO_2 (100 g) column using gradient of EtOAc in hexane from 0 % to 100 % as eluent to obtain 4.08 g of (−)-*trans*-verbenol ((−)-**9**) (52 %).

(−)-*trans*-Verbenol ((−)-**9**) (4.08 g) was epoxidized in accordance with the procedure of preparation of (+)-**10** (see above) to obtain (−)-*trans*-verbenol epoxide (−)-**10** (3.37 g, 75 %). The ^1H and ^{13}C NMR spectral data of (−)-**10** coincided with those reported in the literature (Ardashov *et al.*, 2011).

The second part of the initial mixture (−)-*cis*-verbenol and (−)-*trans*-verbenol (7.9 g) was combined with the mixture fractions obtained after column chromatography at previous stage (2.5 g), then dissolved in Et_2O (150 ml), and cooled to 0 °C. The solution of $Na_2Cr_2O_7 \times 2H_2O$ (12.2 g) in H_2O (45 ml) and H_2SO_4 (4.6 ml, $d = 1.86$) was

added for 10 min. The reaction mixture was stirred for 1 h at 0 °C, and then 24 h at r.t. Water (100 ml) was added to the system, the layers were separated, and the aqueous phase was extracted with Et_2O (4 × 100 ml). The combined organic extracts were washed with saturated $NaHCO_3$ (100 ml) and brine (100 ml), dried over $MgSO_4$, filtered, and concentrated. The residue was separated on a SiO_2 (50 g) column using gradient of Et_2O in hexane from 0 to 100 % as eluent, to obtain of (−)-verbenone ((−)-**5**) (5.18 g, 51 %).

(−)-Verbenone ((−)-**5**) (5.18 g) was dissolved in MeOH (50 ml) and cooled to 10 °C; then, 35 % H_2O_2 (11 ml) followed by 6 N NaOH (3 ml) was added. The mixture was stirred for 2 h at 12–15 °C, diluted with H_2O (60 ml), and extracted with EtOAc (4 × 35 ml). Organic layers were washed with H_2O (2 × 35 ml), dried over Na_2SO_4, filtrated, and concentrated to give (−)-verbenone epoxide as an intermediate product (4.61 g, 80 %, not shown in Scheme 2).

A solution (−)-verbenone epoxide (4.61 g) in Et_2O (30 ml) was added to a suspension of $LiAlH_4$ (1.14 g) in Et_2O at 0 °C for 10 min with stirring. The mixture was stirred for 3 h at 0 °C, and then H_2O (10 ml) was slowly added. The precipitate was filtered, and filtrate was washed with H_2O (3 × 20 ml) and dried over Na_2CO_3. The solvent was distilled off, and (−)-*cis*-verbenol epoxide ((−)-**1**) (2.89 g, 63 %) was obtained. The ^1H and ^{13}C NMR spectral data of (−)-**1** coincided with those reported in the literature (Il'ina *et al.*, 2007).

3. Reactions of monoterpenoids (+)-10, (+)-1, (−)-10, (−)-1 with aldehydes 3a and 3b: general procedure

An appropriate aldehyde (0.360 g) was added to a suspension of clay K10 (1.52 g) in CH_2Cl_2 (20 ml). A solution of 0.400 g of corresponding verbenol epoxide in CH_2Cl_2 (10 ml) was added dropwise with stirring, and the reaction mixture was stirred for 1 h at r.t. Then, ethyl acetate (20 ml) was added, the catalyst was filtered off, and the solvent was distilled off. The residue was separated on a SiO_2 (8 g) column (hexane: EtOAc 100:0–0:100, then acetone was used as eluent).

(a) Reaction of (+)-*cis*-verbenol epoxide ((+)-1) with 3-methoxy-4-hydroxy-benzaldehyde (3a)

The reaction of epoxide (+)-**1** and aldehyde **3a** gave compounds (+)-**2** (0.184 g, 46 %), (+)-**12** (0.144 g, 36 %), and (2*R*,4a*S*,8*S*,8a*S*)-2-(4-hydroxy-3-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol (**11a**) (0.114 g, 15 %, (4*R*):(4*S*) 3:2). The ^1H and ^{13}C NMR spectral data of (+)-**12** and (+)-**2** coincided with those reported in the literature (Il'ina *et al.*, 2007; Ardashov *et al.*, 2011), and data of **11a** with those of **4a**.

(b) Reaction of (+)-*cis*-verbenol epoxide ((+)-1) with 3-hydroxy-4-methoxy-benzaldehyde (3b)

The reaction of epoxide (+)-**1** and aldehyde **3b** gave compounds (+)-**12** (0.08 g, 20 %), and (2*R*,4a*S*,8*S*,8a*S*)-2-(3-hydroxy-4-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol (**11b**) (0.129 g, 17 %, (4*R*):(4*S*) 3:1). The ^1H and ^{13}C NMR spectral data of **11b** coincided with those of **4b**.

(c) Reaction of (+)-*trans*-verbenol epoxide ((+)-10) with aldehyde 3a

The reaction of epoxide (+)-**10** and aldehyde **3a** gave compounds (+)-**12** (0.180 g, 45 %) and (2*S*,4*R*,4a*S*,8-*S*,8a*R*)-2-(4-hydroxy-3-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol ((4*R*)-**14a**) (0.137 g, 18 %). The ^1H and ^{13}C NMR spectral data of (4*R*)-**14a** coincided with those of (4*S*)-**15a**.

(d) Reaction of (+)-*trans*-verbenol epoxide ((+)-10) with aldehyde 3b

The reaction of epoxide (+)-**10** and aldehyde **3b** gave compounds (+)-**12** (0.132 g, 33 %) and (2*S*,4*R*,4a*S*,8-*S*,8a*R*)-2-(3-hydroxy-4-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol ((4*R*)-**14b**) (0.068 g, 9 %). The ^1H and ^{13}C NMR spectral data of (4*R*)-**14b** coincided with those of (4*S*)-**15b**.

(e) Reaction of (−)-*cis*-verbenol epoxide ((−)-1) with aldehyde 3a

The reaction of epoxide (−)-**1** and aldehyde **3a** gave compounds (−)-**12** (0.056 g, 14 %), **13** (0.044 g, 11 %), and (2*S*,4a*R*,8*R*,8a*R*)-2-(4-hydroxy-3-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol (**4a**) (0.198 g, 26 %, (4*S*):(4*R*) 3:1). The ^1H and ^{13}C NMR spectral data of (−)-**12** and **13** coincided with those reported in the literature (Il'ina *et al.*, 2007; Ardashov *et al.*, 2007). Individual diastereomers (4*R*)-**4a** and (4*S*)-**4a** were obtained using preparative HPLC chromatography.

(2*S*,4*S*,4a*R*,8*R*,8a*R*)-2-(4-Hydroxy-3-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol ((4*S*)-**4a**), ^1H NMR ($CDCl_3$ + CD_3OD) 1.46 (3H, d, J(17,4a) = 0.7 Hz, H-17), 1.59 (1H, ddd, J(4e,4a) = 13.3 Hz, J(4e,3a) = 2.7 Hz, J(4e,6) = 1.2 Hz, H_e-4), 1.74 (3H, td, J(18,7) = 2.0 Hz, J(18,8) = 1.7 Hz, H-18), 1.83 (3H, br.t, J(6,7) = 8.5 Hz, H-6), 1.89 (1H, dd, J(4a,4e) = 13.3 Hz, J(4a,3a) = 12.0 Hz, H_a-4), 2.14 (2H, dm, J(7,6) = 8.5 Hz, H-7), 3.76 (2H, m, H-1, H-10), 3.79 (3H, c, OMe), 4.34 (1H, dd, J(3a,4a) = 12.0 Hz, J(3a,4e) = 2.7 Hz, H_a-3), 5.53 (1H, tq, J(8,7) = 3.8 Hz, J(8,18) = 1.7 Hz, H-8), 6.73 (1H, d, J(15,16) = 8.1 Hz, H-15), 6.75 (1H, dd, J(16,15) = 8.1 Hz, J(16,12) = 1.8 Hz, H-16), 6.85 (1H, d, J(12,16) = 1.8 Hz, H-12). ^{13}C

NMR ($CDCl_3$ + CD_3OD) 78.93 (d, C-1), 77.94 (d, C-3), 43.83 (t, C-4), 70.57 (s, C-5), 39.19 (d, C-6), 23.43 (t, C-7), 124.40 (d, C-8), 132.42 (s, C-9), 70.89 (d, C-10), 135.03 (s, C-11), 110.43 (d, C-12), 147.59 (s, C-13), 146.31 (s, C-14), 115.12 (d, C-15), 119.29 (d, C-16), 27.36 (q, C-17), 21.11 (q, C-18), 56.10 (q, OMe). HR-MS: 320.1608 (M^+, $C_{18}H_{24}O_5$; calc 320.1618).

(2*S*,4a*R*,4*R*,8a*R*,8*R*)-2-(4-Hydroxy-3-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol ((4*R*)-**4a**), ^{1}H NMR ($CDCl_3$) 1.16 (3H, s, H-17), 1.55 (1H, ddd, *J*(4e,4a) = 14.0 Hz, *J*(4e,3a) = 3.0 Hz, *J*(4e,6) = 1.3 Hz, H_e-4), 1.66 (1H, dd, *J*(4a,4e) = 14.0 Hz, *J*(4a,3a) = 11.5 Hz, H_a-4), 1.68 (1H, br.t, *J*(6,7) = 8.5 Hz, H-6), 1.74 (3H, td, *J*(18,7) = 2.0 Hz, *J*(18,8) = 1.7 Hz, H-18), 1.93 (2H, dm, *J*(7,6) = 8.5 Hz, H-7), 3.77 (1H, br.s, H_e-10), 3.78 (3H, s, OMe), 4.18 (1H, dd, *J*(1e,10e) = 2.5 Hz, *J*(1e,6a) = 2.0 Hz, H_e-1), 4.64 (1H, dd, *J*(3a,4a) = 11.5 Hz, *J*(3a,4e) = 3.0 Hz, H_a-3), 5.47 (1H, tq, *J*(8,7) = 3.8 Hz, *J*(8,18) = 1.7 Hz, H-8), 6.59 (br.s, OH-C(14)), 6.69-6.72 (2H, m, H-15, H-16), 6.76 (1H, br.s, H-12). ^{13}C NMR ($CDCl_3$) 75.71 (d, C-1), 75.80 (d, C-3), 42.42 (t, C-4), 70.27 (s, C-5), 37.99 (d, C-6), 24.76 (t, C-7), 123.44 (d, C-8), 132.48 (s, C-9), 70.47 (d, C-10), 134.98 (s, C-11), 109.50 (d, C-12), 146.81 (s, C-13), 145.36 (s, C-14), 114.50 (d, C-15), 118.81 (d, C-16), 28.24 (q, C-17), 20.97 (q, C-18), 55.81 (q, OMe). HR-MS: 320.1608 (M^+, $C_{18}H_{24}O_5$; calc 320.1618).

(f) Reaction of (−)-*cis*-verbenol epoxide ((−)-1) with aldehyde 3b

The reaction of epoxide (−)-**1** and aldehyde **3b** gave compounds (−)-**12** (0.048 g, 12 %), **13** (0.052 g, 13 %), and (2*S*,4a*R*,8*R*,8a*R*)-2-(4-hydroxy-3-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol (**4b**) (0.114 g, 15 %, (4*S*):(4*R*) 3:1). Individual diastereomers (4*R*)-**4b** and (4*S*)-**4b** were obtained using preparative HPLC chromatography.

(2*S*,4*S*,4a*R*,8*R*,8a*R*)-2-(3-Hydroxy-4-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol ((4*S*)-**4b**). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 1.49 (3H, d, *J*(17,4a) = 0.8 Hz, H-17); 1.63 (1H, ddd, *J*(4e,4a) = 13.4 Hz, *J*(4e,3a) = 2.7 Hz, *J*(4e,6) = 1.2 Hz, H_e-4); 1.79 (3H, m, H-18); 1.77-1.82 (1H, m, H_a-6); 1.88 (1H, dd, *J*(4a,4e) = 13.4 Hz, *J*(4a,3a) = 12.0 Hz, H_a-4); 2.15 (2H, dm, *J*(7,6) = 8.5 Hz, H-7); 3.77 (1H, dd, *J*(1e,10e) = 2.4 Hz, *J*(1e,6a) = 2.0 Hz, H_e-1); 3.83 (3H, s, OMe); 3.89 (1H, br.d, *J*(10e,1e) = 2.4 Hz, H_e-10); 4.32 (1H, dd, *J*(3a,4a) = 12.0 Hz, *J*(3a,4e) = 2.7 Hz, H_a-3); 5.62 (1H, tq, *J*(8,7) = 3.8 Hz, *J*(8,18) = 1.5 Hz, H-8); 6.73-6.79 (2H, m, H-15, H-16); 6.88-6.91 (1H, m, H-12). ^{13}C-NMR ($CDCl_3$ + CD_3OD): 77.60 (d, C-1); 77.20 (d, C-3); 43.13 (t, C-4); 71.12 (s, C-5); 38.37 (d, C-6); 22.66 (t, C-7); 124.61 (d, C-8); 131.37 (s, C-9); 70.59 (d, C-10); 135.34 (s, C-11); 112.45 (d, C-12); 145.51 (s, C-13); 146.03 (s, C-14); 110.45 (d, C-15); 117.52 (d, C-16); 26.99 (q, C-17); 20.64 (q, C-18); 55.93 (q, OMe). HR-MS: 320.1615 (M^+, $C_{18}H_{24}O_5$; calc 320.1618)

(2*S*,4*R*,4a*R*,8*R*,8a*R*)-2-(3-Hydroxy-4-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol ((4*R*)-**4b**). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 1.21 (3H, s, H-17); 1.59 (1H, ddd, *J*(4e,4a) = 14.2 Hz, *J*(4e,3a) = 2.9 Hz, *J*(4e,6a) = 1.4 Hz, H_e-4); 1.67 (1H, br.t, *J*(6a,7) = 8.7 Hz, H_a-6); 1.74 (1H, dd, *J*(4a,4e) = 14.2 Hz, *J*(4a,3a) = 11.7 Hz, H_a-4); 1.79 (3H, m, H-18); 1.97-2.02 (2H, m, H-7); 3.82 (3H, s, OMe); 3.91 (1H, br.s, H_e-10); 4.21 (1H, dd, *J*(1e,10e) = 2.5 Hz, *J*(1e,6a) = 2.0 Hz, H_e-1); 4.68 (1H, dd, *J*(3a,4a) = 11.7 Hz, *J*(3a,4e) = 2.9 Hz, H_a-3); 5.56 (1H, m, H-8), 5.67 (1H, br.s, OH-C(13)); 6.73-6.79 (2H, m, H-15, H-16); 6.88-6.91 (1H, m, H-12). ^{13}C-NMR ($CDCl_3$ + CD_3OD): 75.11 (d, C-1); 75.41 (d, C-3); 42.08 (t, C-4); 70.85 (s, C-5); 38.10 (d, C-6); 24.58 (t, C-7); 123.97 (d, C-8); 131.87 (s, C-9); 70.57 (d, C-10); 136.03 (s, C-11); 112.40 (d, C-12); 145.48 (s, C-13); 145.87 (s, C-14); 110.45 (d, C-15); 117.57 (d, C-16); 28.33 (q, C-17); 20.74 (q, C-18); 55.93 (q, C-19). HR-MS: 320.1615 (M^+, $C_{18}H_{24}O_5$; calc 320.1618)

(g) Reaction of (−)-*trans*-verbenol epoxide ((−)-10) with aldehyde 3a

The reaction of epoxide (−)-**10** and aldehyde **3a** gave compounds (−)-**12** (0.05 g, 12 %) and (2*R*,4*S*,4a*R*,8*R*,8a*S*)-2-(4-hydroxy-3-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol ((4*S*)-**15a**) (0.114 g, 15 %).

(2*R*,4*S*,4a*R*,8*R*,8a*S*)-2-(4-Hydroxy-3-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol ((4*S*)-**15a**). ^{1}H-NMR ($CDCl_3$): 1.31 (3H, s, H-17); 1.79 (1H, ddq, *J*(4a,4e) = 12.8 Hz, *J*(4a,3a) = 11.7 Hz, *J*(4a,17) = 0.7 Hz, H_a-4); 1.81 (3H, m, all $J \leq 2.5$, H-18); 1.82–1.91 (1H, m, H_a-7); 1.92 (1H, dd, *J*(4e,4a) = 12.8 Hz, *J*(4e,3a) = 2.1 Hz, H_e-4); 1.99 (1H, ddd, *J*(6a,1a) = 11.4 Hz, *J*(6a,7a) = 11.2 Hz, *J*(6a,7e) = 5.0 Hz, H_a-6); 2.33 (1H, dddq, *J*(7e,7a) = 17.4 Hz, *J*(7e,8) = 5.3 Hz, *J*(7e,6a) = 5.0 Hz, *J*(7e,18) = 1.4 Hz, H_e-7); 3.47 (1H, dd, *J*(1a,6a) = 11.4 Hz, *J*(1a,10e) = 4.0 Hz, H_a-1); 3.86 (3H, s, OMe); 4.05 (1H, d, *J*(10e,1a) = 4.0 Hz, H_e-10); 4.49 (1H, dd, *J*(3a,4a) = 11.7 Hz, *J*(3a,4e) = 2.1 Hz, H_a-3); 5.59 (1H, dm, *J*(8,7e) = 5.3 Hz, H-8); 5.69 (1H, br.s, OH-C(14)); 6.82 (1H, dd, *J*(16,15) = 8.1 Hz, *J*(16,12) = 1.8 Hz, H-16); 6.85 (1H, d, *J*(12,16) = 1.8 Hz, H-12); 6.86 (1H, d, *J*(15,16) = 8.1 Hz, H-15). ^{13}C-NMR ($CDCl_3$): 76.99 (d, C-1); 76.44 (d, C-3); 49.80 (t, C-4); 70.51 (s, C-5); 40.62 (d, C-6); 23.95 (t, C-7); 124.41 (d, C-8); 132.58 (s, C-9); 69.12 (d, C-10); 133.58 (s, C-11); 108.78 (d, C-12); 145.36, 146.50 (2 s, C-13, C-14); 114.27 (d, C-15)); 119.08 (d,

C-16); 21.30 (q, C-17); 20.97 (q, C-18); 55.86 (q, OMe). HR-MS: 320.1615 (M^+, $C_{18}H_{24}O_5$; calc 320.1618). $[\alpha]_D^{26} = -20.3$ (c 0.94; $CHCl_3$).

(h) Reaction of (−)-*trans*-verbenol epoxide ((−)-10) with aldehyde 3b

The reaction of epoxide (−)-**10** and aldehyde **3b** gave compounds (−)-**12** (0.048 g, 12 %) and (2*R*,4*S*,4a*R*,8-*R*,8a*S*)-2-(3-hydroxy-4-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol ((4*S*)-**15b**) (0.061 g, 8 %).

(2*R*,4*S*,4a*R*,8*R*,8a*S*)-2-(3-Hydroxy-4-methoxyphenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2*H*-chromene-4,8-diol ((4*S*)-**15b**). ^{1}H-NMR ($CDCl_3$ + CD_3OD): 1.21 (3H, s, H-17); 1.72 (3H, m, all $J \leq 2.5$ Hz, H-18); 1.73 (1H, dd, J(4a,4e) = 12.8 Hz, J(4a,3a) = 11.6 Hz, H_a-4); 1.81 (1H, dd, J(4e,4a) = 12.8 Hz, J(4e,3a) = 2.2 Hz, H_e-4); 1.75-1.85 (1H, m, H_a-7); 1.87 (1H, ddd, J(6a,1a) = 11.2 Hz, J(6a,7a) = 10.8 Hz, J(6a,7e) = 4.5 Hz, H_a-6); 2.26 (1H, dddq, J(7e,7a) = 17.2 Hz, J(7e,8) = 5.2 Hz, J(7e,6a) = 4.5 Hz, J(7e,18) = 1.3 Hz, H_e-7); 3.39 (1H, dd, J(1a,6a) = 11.2 Hz, J(1a,10e) = 3.9 Hz, H_a-1); 3.78 (3H, s, OMe); 3.94 (1H, d, J(10e,1a) = 3.9 Hz, H_e-10); 4.38 (1H, dd, J(3a,4a) = 11.6 Hz, J(3a,4e) = 2.2 Hz, H_a-3); 5.53 (1H, ddq, J(8,7e) = 5.2 Hz, J(8,7a) = 2.5 Hz, J(8,18) = 1.5 Hz, H-8); 6.72 (1H, dd, J(16,15) = 8.2 Hz, J(16,12) = 1.8 Hz, H-16); 6.74 (1H, d, J(15,16) = 8.2 Hz, H-15); 6.85 (1H, d, J(12,16) = 1.8 Hz, H-12). ^{13}C-NMR ($CDCl_3$ + CD_3OD): 76.82 (d, C-1); 76.09 (d, C-3); 49.23 (t, C-4); 69.95 (s, C-5); 40.08 (d, C-6); 23.86 (t, C-7); 124.76 (d, C-8); 132.04 (s, C-9); 69.03 (d, C-10); 134.68 (s, C-11); 112.62 (d, C-12); 145.65, 146.55 (2 s, C-13, C-14); 110.73 (d, C-15); 117.49 (d, C-16); 20.73 (q, C-17); 20.70 (q, C-18); 55.73 (q, OMe). HR-MS: 320.1622 (M^+, $C_{18}H_{24}O_5$; calc 320.1618).

Biology

Animals

All studies were carried out on non-breeding albino mice (male) weighing 20–25 g, eight animals in each group (SPF-vivarium of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences). Mice were maintained at 22–25 °C on a 12-h light–dark cycle with food and water available ad libitum. All work with animals was performed in strict accordance with the legislation of the Russian Federation, the regulations of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, and the requirements and recommendations of the Guide for the Care and Use of Laboratory Animals.

Acetic acid abdominal constriction Studied compounds and diclofenac sodium were dissolved in saline containing 0.5 % Tween 80 just before use and were administered per os in a dose of 10 mg/kg 1 h before testing. Control group of mice was given saline containing 0.5 % Tween 80 1 h before testing. Analgesic activity was assessed using writhing test induced by acetic acid. Pain reaction was determined by the number of abdominal writhing movements, recorded from the fifth to the eighth minute after acetic acid injection (0.75 %, 0.1 ml/mouse) (Koster *et al.*, 1959). The percentage of pain reaction inhibition was calculated according to the following equation: % inhibition = $100 \times (A - B)/A$, where A is the mean number of writhes in the control group and B is the mean number of writhes in the test group. The effectiveness of the studied compounds was evaluated according to their ability to reduce the number of writhing test induced by administration of acetic acid.

Statistical data processing was carried out by a Statistica 8.0 program.

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