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Synthesis of Isomeric 1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonanes and 1'-Hydroxybrevicomin from Ethyl 5-Oxohexenoate Ethyleneacetal through Cyclopropanation of an Ester Group Followed by Oxidative Opening of the Three-Membered Ring

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Abstract—Syntheses were performed of (±)-*endo*-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane and (±)-1'-hydroxy-*exo*-brevicomin constituting racemic forms of the secretion components of pine weever (*Hylobius abietis*) and bark beetle of upland pines (*Dendroctonus ponderosae*) through cyclopropanation of the ester group of an available ethyl 5-oxohexanoate ethyleneacetal with the subsequent oxidative opening of the three-membered ring in the compound obtained.

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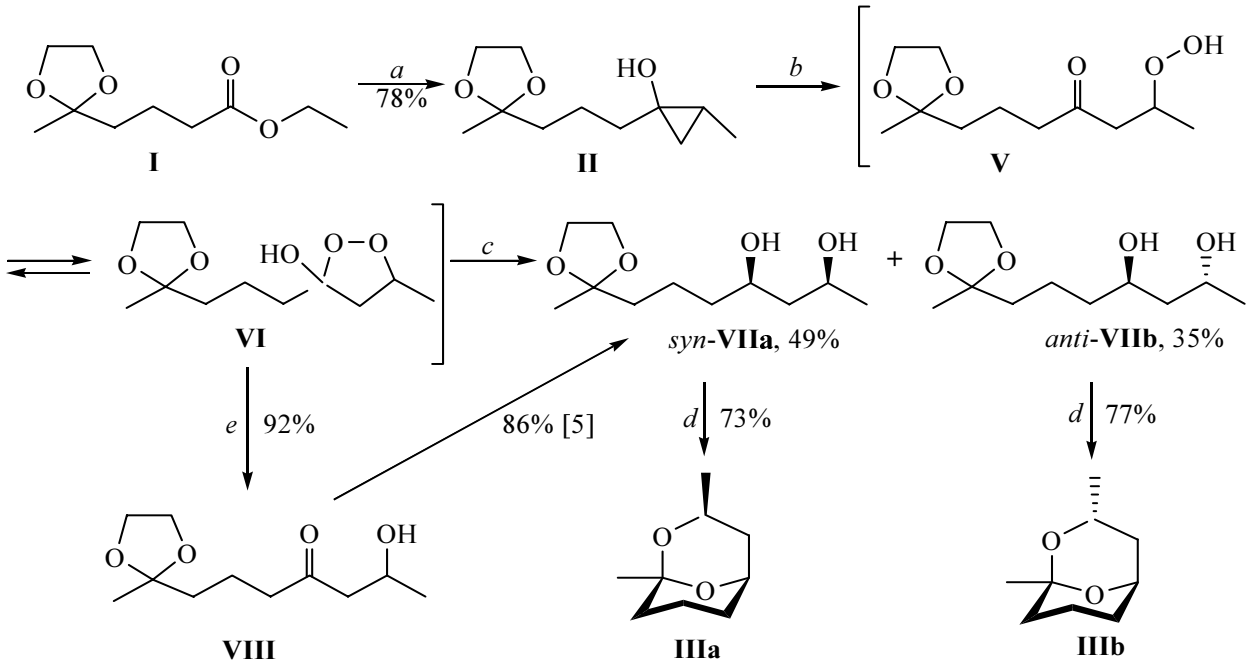
We recently developed an efficient procedure for preparation of α,β epoxyketones consisting in successive reactions of cyclopropanation of aliphatic carboxylic acids esters with alkylmagnesium halides in the presence of Ti(IV) alkoxides [1], oxydation of the arising 1-alkylcyclopropanols with molecular oxygen catalyzed by Mn(II) [2] to β-hydroxyperoxyketones, and dehydration of the latter under the treatment with potassium hydroxide [3]. This approach proved also to be convenient for the synthesis of epoxy-1,4-dicarbonyl compounds whose intramolecular acetalization into derivatives of 6,8-dioxabicyclo-[3.2.1]octane was applied to the preparation of racemic forms of pheromones of spruce and pine beetles belonging to the species *Dendroctonus* and *Dryocoetes*: *endo*-brevicomin, *endo*-isobrevicomin, and frontalin [4].

In this paper we report on the synthesis from an available ethyleneacetal of ethyl 5-oxohexanoate (**I**) [5] of substituted cyclopropanol **II** and its conversion into (±)-*endo*-1,3-dimethyl-2,9-dioxabicyclo-[3.3.1]nonane (**IIIa**), its (±)-*exo*-isomer **IIIb**, and (±)-1'-hydroxy-*exo*-brevicomin (**IV**). Compound **IIIa**, a structural isomer of the brevicomin [6], was discovered in the bark of trees ecized by pine timber beetles *Trypodendron lineatum* [7] and later was identified in the secretion of the pine weever (*Hylobius abietis*) [6] and the bark beetle of upland pines (*Dendroctonus ponderosae*) [8] whereas the hydroxylated brevicomin (**IV**) proved to be the second main component after *exo*-brevicomin in the secretion of the males of *D. ponderosae* [8]. Compound **IIIa** and its *exo*-isomer **IIIb** were objects of numerous chemical syntheses demonstrating as a rule different approaches to the building up of *syn*- or *anti*-1,3-diol moieties [9]. For the preparation of compound **IV** and its stereoisomers synthetic schemes were advanced where the key stages were the enantioselective versions of epoxydation [8] and dehydroxylation [10], and also of aldol condensation [11].

Ester **I** containing a protected carbonyl group in the δ-position reacted with 3.5 equiv of propylmagnesium bromide in the presence of the catalytic quantity of titanium(IV) isopropoxide afforded in a good yield a *cis*-1,2-disubstituted cyclopropanol **II**. According to the ^{1}H NMR data the diastereoselectivity of the conversion exceeded 94%, and the *cis*-position of the alkyl substituents in the cyclopropanol **II** was in agreement with the data on the stereochemistry of this reaction [2–4]. The oxidation of cyclopropanol **II** with the air oxygen in the presence of manganese abietate in benzene resulted in β-hydroxyperoxyketone **V** that existed in an equilibrium with a cyclic form **VI** [3]. On replacing the solvent with ethyl ether peroxide **V** without additional purification was subjected to a reduction with lithium aluminum hydride



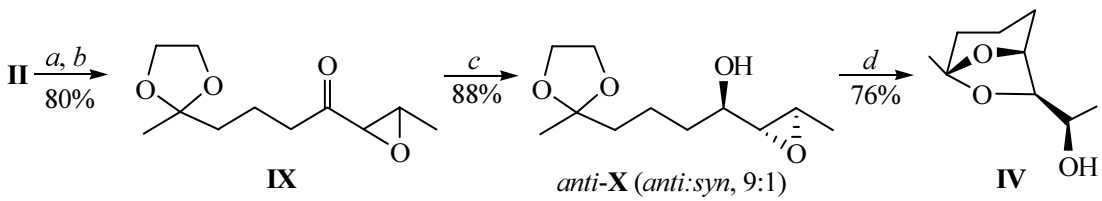
a – 3.5 equiv of PrMgBr, 20 mol% of $Ti(OPr\text{-}i)_4$, ether–THF, 2:3; *b* – O_2, 1 mol%, C_6H_6; *c* – $LiAlH_4$, ether, 0°C; *d* – H_2SO_4, CCl_4; *e* – PPh_3, ether.

to furnish a mixture of *syn*- and *anti*-1,3-diols **VIIa** and **VIIb**, ~4:3, which was readily separated by column chromatography on silica gel. In the ^1H NMR spectrum of compound **VIIa** the signals of the methine protons from the diol fragment appear upfield reative to the corresponding signals in the spectrum of the *anti*-isomer **VIIb**; this feature is characteristic of stereomers of 1,3-diols with similar structure [12, 13]. The treatment of compounds **VIIa** and **VIIb** with 50% sulfuric acid afforded *endo*-(**IIIa**) and *exo*-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane (**IIIb**) in yields calculated on cyclopropanol **II** equal to 36 and 27% respectively. Note that the cyclization of thus obtained mixtures of diols **VIIa** and **VIIb** afforded a mixture of *endo*- and *exo*-isomers **IIIa** and **IIIb** which also were easily separated by column chromatography (yields with respect to compound **II** 24 and 18%].

The reduction of peroxide **V** with sodium borohydride in THF afforded in a 80% yield a mixture of *syn*- and *anti*-diols **VIIa** and **VIIb** with a little prevalence of the latter (*anti*-**VIIb**/*syn*-**VIIa** ~ 4:3]. We unsuccessfully attempted to increase the *syn*-selectivity of the reduction of peroxyketone **V** with hydrides by addition of chelating substances, although this approach had given good results in the preparation of *syn*-1,3-diols from β-hydroxyketones [5, 14]. In particular, the reduction of peroxide **V** with the sodium borohydride or the lithium aluminum hydride in the presence of magnesium bromide gave rise to complex mixtures of substances. At the same time by the deoxygenation of peroxide **V** with triphenylphosphine we cleanly prepared ketol **VIII** whose stereoselective reduction with sodium borohydride to *syn*-diol **VIIa** in the presence of diethylmethoxyborane was described in [5].

Compound **II** also turned out to be a convenient starting material for the synthesis of *exo*-brevicomin derivative hydroxy-substituted in the side chain **IV,** the process was carried out in keeping with the given scheme.

The treatment with a water solution of potassium hydroxide of the reaction mixture obtained by oxidation of cyclopropanol **II** with air oxygen in the presence



a – O_2, 1 mol% of Mn(II) abietate, C_6H_6; *b* – KOH, H_2O; *c* – $LiAl(OBu\text{-}t)_3H$, ether, –78°C; *d* – HBF_4, CH_3CN

of manganese(II) abietate afforded in a high yield α,β-epoxyketone **IX** with a *trans*-location of substituents in the three-membered ring as shown by the value of the coupling constant of 2 Hz for the vicinal hydrogen atoms of the epoxy ring [3]. The reduction of epoxyketone **IX** with lithium tris-*tert*-butoxyaluminohydride in ether at –78°C occurred with the expected stereodirection [15] and gave predominantly *anti*-epoxyalcohol **X**. The stereoisomers ratio in compound **X** (*anti:syn,* 9:1), was established from the intensity ratio in the ^{1}H NMR spectrum of the corresponding signals of the epoxy ring protons. The configuration of the major isomer **X** is established based on the small coupling constant between the protons at the α-carbon of the epoxy ring and the carbinol group(*J* 3.1 Hz); this feature is characteristic of the *anti*-epoxyalcohols of similar structure [8]. The cyclization of compound **X** in the presence of HBF_4 furnished in a good yield the target 1'-hydroxy-*exo*-brevicomin (**IV**) (54% calculated on cyclopropanol **II**). The ^{1}H NMR spectrum of compound obtained was identical to the published spectra and showed that the amount of the corresponding *endo*-isomer impurity in compound **IV** isolated by means of column chromatography did not exceed 5% [8, 10].

Consequently we have developed a simple and convenient preparation procedure for substituted bicyclic acetals **IIIa** and **IV** which are racemic forms of pheromone components of the insect pests of coniferous forests [16, 17], starting from available ethyl 5-oxohexanoate ethyleneacetal through the key stages of ester group cyclopropanation, subsequent oxidative opening of the there-membered ring, and intramolecular cyclizations of the products obtained by hydride reduction of the formed intermediates

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra of compounds solutions in $CDCl_3$ were registered on a spectrometer Bruker AC-400 at operating frequencies 400 and 100 MHz respectively. IR spectra were recorded on a spectrophotometer Specord 75IR from solutions of compounds in CCl_4. Ethyl ether, tetrahydrofuran, and benzene were dried and distilled over sodium metal.

(1*RS*,2*RS*)-2-Methyl-1-[3-(2-methyl-1,3-dioxolan-2-yl)propyl]cyclopropanol (II). To a stirred solution of 10 mmol (2.02 g) of ester **I** and 2 mmol (0.6 ml) of titanium(IV) isopropoxide in 12 ml of anhydrous THF was added dropwise within 2 h a solution of 40 mmol of propylmagnesium bromide in a mixture of 12 ml of anhydrous ethyl ether and 10 ml of THF. The reaction mixture was stirred for 1 h at room temperature, then it was cooled with ice water and treated with 5% water solution of NaOH (10 ml). The precipitate was filtered off and washed with ether. The ether layer was separated, and products were extracted from the water layer into ether. The combined ether solutions were washed with a saturated NaCl solution and dried with sodium sulfate. The solvent was distilled off in a vacuum, and the reaction product was purified by distillation under a reduced pressure. Yield 1.56 g (78%), bp 102–104°C (2 mm Hg). IR spectrum, cm^{-1}: 3599, 3438 (OH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: –0.03–0.02 m (1H), 0.74–0.81 m (1H), 0.86–0.91 m (1H), 0.98 d (3H, *J* 2.2 Hz), 1.30 s (3H), 1.33–1.72 m (6H), 2.47 br.s (1H), 3.87–3.95 m (4H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.18, 19.43, 20.20, 20.61, 23.72, 33.79, 38.93, 58.37, 64.54, 110.12. Found, %: C 65.73; H 10.16. $C_{11}H_{20}O_3$. Calculated, %: C 65.97; H 10.07.

Substituted 1,3-diols VIIa and VIIb. Through a solution of 2 mmol (0.40 g) of cyclopropanol **II** and 0.02 mmol (0.013 g) of Mn(II) abietate in 15 ml of benzene at vigorous stirring was passed a stream of air till a complete disappearance of the initial compound (about 1 h, TLC monitoring). The solvent was distilled off, the residue was dissolved in anhydrous ethyl ether (5 ml). The solution obtained was added dropwise at 0°C to a dispersion of 2 mmol (0.076 g) of lithium aluminum hydride in 5 ml of ethyl ether, and the reaction mixture was stirred for 2 h at room temperature. Then the reaction mixture was treated in succession with 0.08 ml of water, 0.08 ml of 15% water solution of NaOH, and 0.23 ml of water. The precipitate formed was filtered off, the filtrate was dried over sodium sulfate, the solvent was distilled off in a vacuum, and the resulting mixture of diols **VIIa** and **VIIb** was separated by column chromatography on silica gel with gradient elution by a mixture ethyl acetate–petroleum ether, from 1:1 to 100:0.

(2*RS*,4*SR*)-7-(2-Methyl-1,3-dioxolan-2-yl)-heptane-2,4-diol (VIIa) [9]. Yield 0.21 g (49%). IR spectrum, cm^{-1}: 3398 (OH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 d (3H, *J* 6.1 Hz), 1.29 s (3H), 1.35–1.59 m (6H), 1.60–1.68 m (2H), 3.20 br.s (2H), 3.79–3.87 m (1H), 3.87–3.96 m (4H), 3.97–4.06 m (1H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 19.70, 23.67, 24.08, 38.13, 38.86, 44.56, 64.54, 68.95, 72.65, 110.01.

(2*RS*,4*RS*)-7-(2-Methyl-1,3-dioxolan-2-yl)heptane-2,4-diol (VIIb) [16]. Yield 0.15 g (35%). IR spectrum, cm^{-1}: 3385 (OH). ^{1}H NMR spectrum

($CDCl_3$), δ, ppm: 1.19 d (3H, *J* 6.7 Hz), 1.28 s (3H), 1.33–1.57 m (6H), 1.58–1.68 m (2H), 3.16 br.s (2H), 3.86–3.95 m (5H), 4.05–4.15 m (1H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.13, 23.47, 23.69, 37.42, 38.90, 44.09, 64.56, 65.33, 68.94, 110.02.

(±)-*endo*-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]-nonane (IIIa). To a solution of 2 mmol (0.44 g) of diol **VIIa** in 20 ml of tetrachloromethane was added 3 ml of 50% sulfuric acid, and the mixture was vigorously stirred for 1.5 h. The organic layer was separated, the products were extracted from the water layer into tetrachloromethane (3×2 ml). The combined organic solutions were washed with a saturated solution of $NaHCO_3$ and dried over sodium sulfate. The solvent was distilled off at the atmospheric pressure, and the residue was subjected to column chromatography on silica gel (eluent ethyl ether–pentane, 5:95). Yield 0.23 g (73%). The spectral characteristics of the compound obtained were in agreement with the published data [5].

(±)-*exo*-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]-nonane (IIIb) was prepared as described above. Yield 0.24 g (77%). The spectral characteristics of the compound obtained were in agreement with the published data [18].

5-Hydroxy-1-(2-methyl-1,3-dioxolan-2-yl)-heptan-3-one (VIII) [5]. Through a solution of 2 mmol (0.40 g) of cyclopropanol **II** and 0.02 mmol (0.013 g) of Mn(II) abietate in 15 ml of benzene at vigorous stirring was passed a stream of air till a complete disappearance of the initial compound (about 1 h, TLC monitoring). The solvent was distilled off, the residue was dissolved in anhydrous ethyl ether (10 ml), and 2 mmol (0.52 g) of triphenylphosphine was added thereto in one portion. The reaction mixture was stirred for 3 h, passed through a small bed of silica gel, and the solvent was distilled off in a vacuum. The residue was subjected to column chromatography on silica gel with gradient elution by a mixture ethyl acetate–petroleum ether, from 3:1 to 1:2. Yield 0.40 g (92%). IR spectrum, cm^{-1}: 3465 (OH), 1725 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 d (3H, *J* 6.5 Hz), 1.30 s (3H), 1.58–1.73 m (4H), 2.42 t (2H, *J* 6.7 Hz), 2.49–2.61 m (2H), 3.2 br.s (1H), 3.85–3.97 m (4H), 4.16–4.25 m (1H).

4-(2-Methyl-1,3-dioxolan-2-yl)-1-[(2*RS*,3*SR*)-3-methyloxiranyl]butan-1-one (IX). Through a solution of 10 mmol (2.00 g) of cyclopropanol **II** and 0.1 mmol (0.066 g) of Mn(II) abietate in 75 ml of benzene at vigorous stirring was passed a stream of air till a complete disappearance of the initial compound (about 1 h, TLC monitoring). To the mixture obtained was added 4 ml of 0.5 M KOH water solution, and the reaction mixture was stirred for 1–2 h at room temperature. The reaction mixture was filtered, the organic layer was separated, washed with a saturated solution of NaCl, and dried over Na_2SO_4. On removing the solvent the residue was distilled at a reduced pressure. Yield 1.71 g (80%), bp 103–105°C (2 mm Hg). IR spectrum, cm^{-1}: 1712 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 s (3H), 1.38 d (3H, *J* 5.1 Hz), 1.56–1.70 m (4H), 2.29 d.d.d (1H, J_1 17.9, J_2 7.6, J_3 6.6 Hz), 2.44 d.d.d (1H, J_1 17.9, J_2 7.2, J_3 6.6 Hz), 3.10 q.d (1H, J_1 5.1, J_2 2.0 Hz), 3.15 d (1H, *J* 2.0 Hz), 3.85–3.95 m (4H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.41, 17.45, 23.59, 36.84, 38.00, 54.12, 60.42, 64.47, 109.62, 207.30. Found, %: C 61.52; H 8.39. $C_{11}H_{18}O_4$. Calculated, %: C 61.66; H 8.47.

(1*RS*)-4-(2-Methyl-1,3-dioxolan-2-yl-1-[(2*RS*,3*RS*)-3-methyloxiranyl]butan-1-ol (X). To a suspension of $LiAl(OBu\text{-}t)_3H$ obtained from 0.38 g (10 mmol) of $LiAlH_4$ and 2.22 g (30 mmol) *tert*-butanol in 10 ml of anhydrous ethyl ether at cooling to –78°C was added dropwise a solution of 3 mmol (0.64 g) of epoxyketone **IX** in 5 ml of the same solvent. The reaction mixture at stirring was slowly warmed to 0°C (within about 3 h), then it was treated in succession with 0.38 ml of water, 0.38 ml of 15% NaOH solution, and 1.14 ml of water. The precipitate was separated, washed with ether, and the ether layer was dried over sodium sulfate. After removing solvent in a vacuum the reaction product was purified by column chromatography on silica gel with gradient elution by a mixture ethyl acetate–petroleum ether, from 3:1 to 1:1. Yield 0.57 g (88%) (ratio of *anti*- and *syn*-isomers 9:1). IR spectrum, cm^{-1}: 3465 (OH). ^1H NMR spectrum of *anti*-(**X**) ($CDCl_3$), δ, ppm: 1.31 s (3H), 1.32 d (3H, *J* 5.1 Hz), 1.44–1.72 m (6H), 2.72 d.d (1H, J_1 3.1, J_2 2.6 Hz), 3.07 q.d (1H, J_1 5.1, J_2 2.6 Hz), 1.93 br.s (1H), 3.74–3.79 m (1H), 3.88–3.98 m (4H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.21, 19.85, 23.71, 33.53, 39.01, 51.00, 61.76, 64.60, 68.64, 109.94. Found, %: C 61.31; H 9.28. $C_{11}H_{20}O_4$. Calculated, %: C 61.09; H 9.32.

(1*RS*)-1-{(1*RS*,5*RS*,7*RS*)-5-Methyl-6,8-dioxabicyclo[3.2.1]oct-7-yl}ethanol (IV). A solution of 2 mmol (0.43 g) of epoxyalcohol **X** and 0.1 g of concn. HBF_4 in 25 ml of anhydrous acetonitrile was stirred at room temperature till a complete disappearance of the initial compound (about 1 h, TLC monitoring). Then the reaction mixture was treated with 10% solution of $NaHCO_3$ (25 ml), the reaction product was extracted with

dichloromethane (5×15 ml), and dried with sodium sulfate. The solvent was distilled off in a vacuum, the residue was subjected to column chromatography on silica gel with gradient elution by a mixture ethyl acetate–petroleum ether, from 3:1 to 1:1. Yield 0.26 g (76%). The spectral characteristics of the compound obtained were in agreement with the published data [8].

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