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A convenient route to 1-(2-oxiranyl)-1,4-diketones and their application to the synthesis of *endo*-brevicomin, *endo*-isobrevicomin, frontalin and related compounds via alkylated 6,8-dioxabicyclo[3.2.1]octan-2-ones

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Abstract—1-(2-Oxiranyl)-1,4-alkanediones were prepared from the ethylene acetals of ethyl 4-oxoalkanoates via the oxidation of the intermediate 1,2-dialkylcyclopropanols having a protected carbonyl group in an aliphatic chain. Intramolecular acetalization of these epoxy dicarbonyl compounds gave alkylated 6,8-dioxabicyclo[3.2.1]octan-2-ones in good yields. The latter were found suitable to be precursors for (±)-*endo*-brevicomin and its 2-hydroxy derivative, as well as (±)-*endo*-isobrevicomin and (±)-frontalin.
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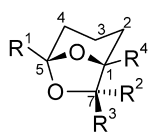
1. Introduction

Alkylated 6,8-dioxabicyclo[3.2.1]octanes play an important role in systems of chemical communication among many bark beetles, which infect pine trees.[1] Brevicomin is a typical pheromone component of *Dendroctonus* and *Dryocoetes* pine beetles, and it is frequently produced by these insects as a mixture of *exo*- and *endo*-diastereomers at C-7 (**1a** and **1b**, Fig. 1), with a large excess of the (+)-*exo*-brevicomin **1a**.[1,2] In contrast to the latter, the enantiomeric excess in the accompanying *endo*-brevicomin **1b** is rarely greater than 70%.[1,2c–e] Both the *exo*- and *endo*-isomers of isobrevicomin (**1c** and **1d**, respectively) were isolated in 1996 by Francke and co-workers[3] as the minor components of the volatiles, obtained from male mountain pine bark beetles, *Dendroctonus ponderosae*. Frontalin **1e** is the aggregation pheromone of southern pine bark beetle, *Dendroctonus frontalis*.[4]



1a R^1 = Me, R^2 = R^4 = H, R^3 = Et (*exo*-brevicomin);
1b R^1 = Me, R^2 = Et, R^3 = R^4 = H (*endo*-brevicomin);
1c R^1 = Et, R^2 = R^4 = H, R^3 = Me (*exo*-isobrevicomin);
1d R^1 = Et, R^2 = Me, R^3 = R^4 = H (*endo*-isobrevicomin);
1e R^1 = R^4 = Me, R^2 = R^3 = H (frontalin)

Figure 1.

Compounds **1a**–**e** all have been the target of numerous syntheses in both racemic and enantiomerically pure form.[1,5,6] The general strategy of these syntheses is the generation of an appropriate 5,6-epoxyketones or corresponding dihydroxyketone, followed by intramolecular acetalization.[1,3,7] Using the deuterated and ^{18}O-labeled *(Z)*-6-nonen-2-one, Vanderwel and Oehlschlager found that this unsaturated ketone serves as a precursor of (+)-*exo*-brevicomin **1a** in the bark beetles *D. ponderosae* Hopkins and that the pheromone biosynthesis proceeds through a *cis*-epoxyketone intermediate, without its conversion to a diol prior to the cyclization stage.[8] For the formation of *endo*-isomers **1b** and **1d**, the corresponding *trans*-epoxides are required.[1,7a] For example, racemic *endo*-isobrevicomin **1d** has been synthesized from the epoxide of *(E)*-7-nonen-3-one.[3]

Recently, we have reported a flexible and convenient method for the preparation of aliphatic α,β-epoxyketones based on a manganese-catalyzed ring cleavage of 1-substituted and 1,2-disubstituted cyclopropanols with gaseous oxygen followed by transformation of the hydroperoxyketone intermediates into the target products, under the action of potassium hydroxide.[9] The simplicity of this one-pot procedure, coupled with facile availability of the corresponding cyclopropanols,[10,11] makes it attractive for the synthesis of epoxyketones bearing an additional functional group in the aliphatic chain. In the present

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work, we wish to describe the application of this methodology to the preparation of 1-(2-oxiranyl)-1,4-diketones **6**, which are then employed in the synthesis of 6,8-dioxabicyclo[3.2.1]octane derivatives, including (±)-*endo*-brevicomin **1b**, (±)-*endo*-isobrevicomin **1d**, (±)-frontalin **1e** and the related hydroxy compounds **8a**, **9a**.

2. Results and discussion

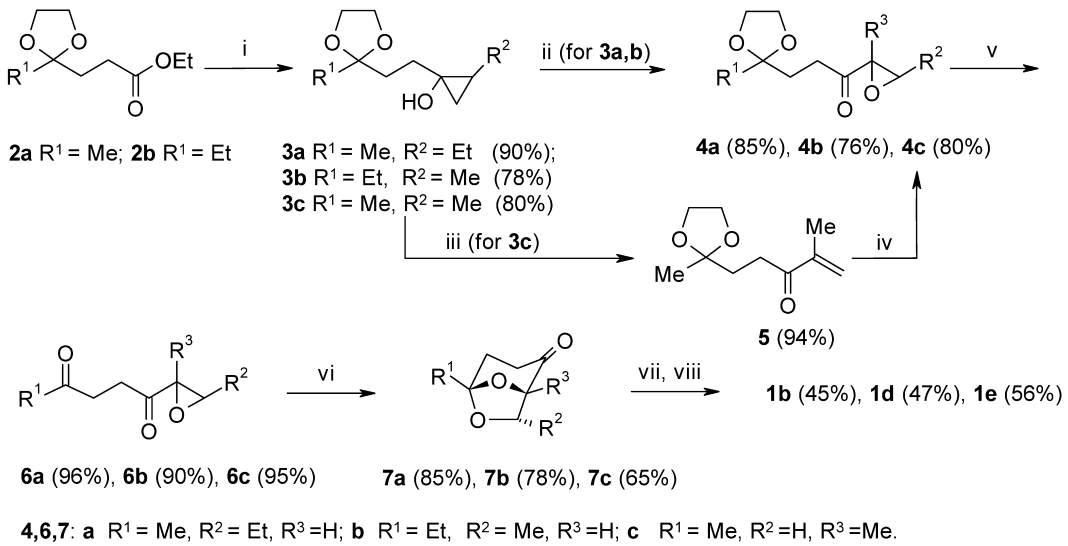
Epoxyketones **4a**,**b**, with an additional protected carbonyl group, have been obtained in two preparative steps in an overall yield of 60–76%, starting from ethylene acetals of ethyl 4-oxoalkanoates **2a**,**b**, via the cyclopropanols **3a**,**b**, as a key intermediates (Scheme 1). The latter were prepared by cyclopropanation of esters **2a**,**b** with butylmagnesium bromide and propylmagnesium bromide, respectively, in the presence of Ti(IV) isopropoxide.[10] This reaction proceeded with high diastereoselectivity (de>94% by ^{1}H NMR spectroscopy). The relative stereochemistry of 1,2-disubstituted cyclopropanols **3a**,**b** was assigned to be *cis* on the basis of literature data.[11] The Mn(II) abietate catalyzed oxidative cleavage of compounds **3a**,**b** with molecular oxygen, followed by treatment of the reaction mixture with aqueous potassium hydroxide, led to the expected products **4a**,**b**, wich exhibit a *trans*-configuration of the oxirane ring.[9]

The synthesis of compound **4c** started with the cyclopropanol **3c**, prepared from the protected ethyl levulinate **2a** and propylmagnesium bromide. Compound **3c** was subjected to the reaction with the bromine–pyridine complex, followed by dehydrobromination of resulting β-bromoketone.[12] The corresponding α,β-unsaturated ketone thus formed was epoxidized without isolation by the action of alkaline hydrogen peroxide[13] to give **4c** in 60% overall yield from **2a** (Scheme 1; steps i, iii, iv).

Attempted transacetalization of compound **4a** into the desired 6,8dioxabicyclo[3.2.1]octan-2-one **7a**, by treatment with 10% aq. H_2SO_4 in diethyl ether, resulted in the formation of a ca. 1:1 mixture of two products, an expected cyclic ketone **7a** and epoxy diketone **6a**. Furthermore, it was proven that no transformation **6a**→**7a** took place during this catalytic process. Therefore, for the preparation of compounds **7a**–**c**, the two-step procedure including deprotection of ketals **4a**–**c** with diluted H_2SO_4 on SiO_2 followed by cyclization of obtained 1-(2-oxiranyl)-1,4-diketones **6a**–**c** under the action of boron trifluoride etherate was found to be more effective (Scheme 1, steps v–vi, 62–82% overall yield of **7a**–**c** from **4a**–**c**). The intramolecular reaction of the *trans*-oxirane moiety with the remote carbonyl group in precursors **6a**,**b** proceeded with high stereoselectivity, the bicyclic *endo*-acetals **7a**,**b** being the single isolated products. The relative configuration of compounds **7a**,**b** was confirmed by comparison of their spectral data with that reported for **7a** and its *exo*-isomer,[14] as well as by subsequent synthetic transformations.

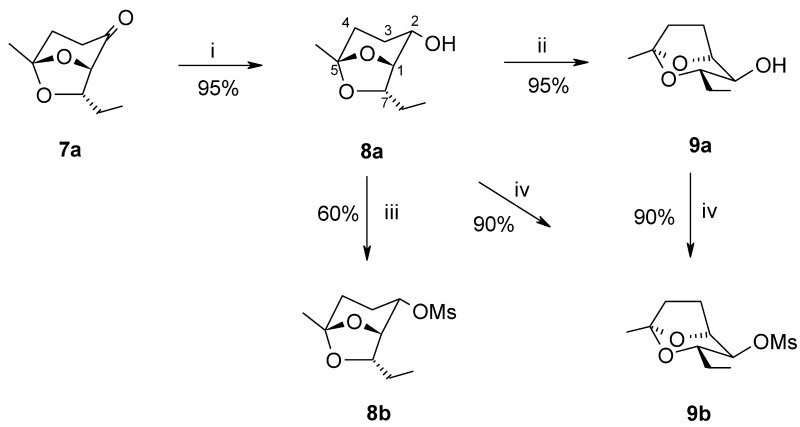
Bicyclic ketones **7a**–**c** have been converted to the racemic *endo*-brevicomin **1b**, *endo*-isobrevicomin **1d**, and frontalin **1e**, respectively, by a conventional deoxygenation method, which was earlier described for the preparation of compounds (±)-**1b**[14] and (+)-**1e**.[15] Each particular ketone **7** was treated with ethanedithiol in the presence of $BF_3{\cdot}OEt_2$ and the resulting cyclic dithioketals were reduced with Raney nickel to furnish the target pheromones. Several other methods known to effect the deoxygenation of ketones or secondary alcohols were tried, but the Wolff–Kishner reaction of ketone **7a**, the reduction of its tosylhydrazone as well as the reduction of mesylate or xanthogenate of alcohol **8a**, failed to give only a trace amount of the desired product.

Compounds **7a**–**c** are potentially suitable starting materials for the synthesis of 2-hydroxylated 6,8-dioxabicyclo[3.2.1]octanes, especially because several isomeric hydroxybrevicomins have been produced by male mountain pine beetles, *D. ponderosae*.[1,3] As anticipated, the reduction of ketone **7a** in an etheral solution, with a slight excess of lithium aluminum hydride, followed by careful addition of



4,6,7: **a** R^1 = Me, R^2 = Et, R^3 =H; **b** R^1 = Et, R^2 = Me, R^3 =H; **c** R^1 = Me, R^2 =H, R^3 =Me.

Scheme 1. *Reagents*: (i) 4 equiv. $R^2CH_2CH_2MgBr$, 20 mol% Ti(O*i*-Pr)$_4$, Et_2O/THF (2:3); (ii) O_2, 1 mol% Mn(II) abietate, PhH, then KOH, H_2O; (iii) Br_2/Py. Et_2O, then Al_2O_3, *n*-C_5H_{12}; (iv) H_2O_2, *i*-PrOH, NaOH; (v) 15% aq. H_2SO_4/SiO_2, CH_2Cl_2; (vi) $BF_3{\cdot}OEt_2$, CH_2Cl_2; (vii) $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (viii) Ni(Ra), EtOH.



Scheme 2. *Reagents*: (i) 0.75 equiv. $LiAlH_4$, Et_2O; then 5% HCl; (ii) *p*-TsOH, benzene; (iii) NaH, THF; then MsCl; (iv) MsCl, Et_3N, Et_2O.

diluted hydrochloric acid (to pH=7–8), afforded the new 2-hydroxy-*endo*-brevicomin **8a** in almost quantitative yield and with a de>95% (Scheme 2). Similarly, reduction of **7a** with (*t*-BuO)$_3$LiAlH or with sodium metal in isopropyl alcohol gave the same compound **8a**, containing an equatorial OH group. The formation of **8a** is probably due to steric hindrance imposed by the *endo*-arranged 7-Et group for equatorial attack on the ketone **7a** with the reducing reagent.

Remarkably, the single compound **9a**, containing 2,8-dioxabicyclo[3.2.1]octane sceleton, was isolated in 95% yield by the reduction of ketone **7a** with $LiAlH_4$ followed by quenching with an excess of aqueous HCl. Compound **9a** was earlier identified by Francke's group[3] as a minor volatile component from *D. ponderosae* males. The reduction of ketone **7a** with $NaBH_4$ in methanol resulted in the formation of a mixture of isomers **8a** and **9a** in the ratio of 1:1. We found, that 2-hydroxy-*endo*-brevicomin **8a** is extremely sensitive to acids, including Lewis acids. Thus, compound **8a** rearranges completely after ca. 3 h to its isomer **9a** in a benzene solution, in the presence of a trace amount of *p*-TsOH at room temperature. This is consistent with the observations of Francke,[3] who was first to suggest that the lability of compound **8a** is a possible explanation of its lack among three other natural diastereomeric 2-hydroxylated brevicomins in *D. ponderosae*. The synthesis of compound **8a** involving an acid-catalyzed ring-closing stage was undertaken by Barbas III, Lerner and co-workers,[16] however, the presented spectral data clearly demonstrate that the product **9a** was isolated instead of the desired and mistakenly reported compound **8a**.

The structure of compound **8a** was confirmed by ^{1}H NMR, ^{13}C NMR and mass spectroscopy, however more evident data on the relative stereochemistry of **8a** have been corroborated by spectral characteristics of its mesylate **8b**. Surprisingly, the reaction of **8a** with mesyl chloride in the presence of Et_3N under standard conditions afforded mesylate **9b** of isomeric alcohol **9a**. This may be due to the rearrangement of starting **8a** or its mesylate **8b** under the action of nascent HCl (or $Et_3NH^+Cl^-$). The mesylate **8b** was prepared by standard treatment of **8a** with NaH and reaction of the subsequent sodium alkoxide with MsCl.

The distinctive characteristic of the ^{1}H NMR spectrum of mesylate **8b** is the large coupling constant of 10.9 Hz between the axial protons at C-3 and at C-2, thus indicating the equatorial position of the OH group in precursor compound **8a**. Additionally, the coupling constant of 3.9 Hz between protons at C-1 and C-7 is in a good agreement with the reported data for related *endo*-bicyclic acetals, as this value differs appreciably from $J_{1,7}<1$ Hz observed for known *exo*-isomers of **8a**.[3]

In conclusion, we have developed effective methods for the preparation of 1-(2-oxiranyl)-1,4-diketones which were easily converted into alkylated 6,8-dioxabicyclo[3.2.1]-octan-2-ones. The latter are versatile precusors of various pheromone components, including racemic *endo*-brevicomin, *endo*-isobrevicomin and frontalin, as well as the unknown 2-hydroxylated *endo*-brevicomin.

3. Experimental

IR spectra were measured on a Specord 75 IR or FT-IR Perkin–Elmer 1000 spectrophotometer. ^{1}H NMR spectra were recorded at 400 MHz (Bruker Avance 400) with $CDCl_3$ or C_6D_6 as a solvent. ^{13}C NMR spectra were recorded with a Bruker Avance 400 at 100.6 MHz with $CDCl_3$ or C_6D_6 as a solvent. Mass spectra were obtained on a Shimadzu QP-5000 GC/MS spectrometer. Melting points were determined in open capillaries and are uncorrected. Preparative column chromatography was carried out on silica gel (Merck; 70–230 mesh). All chemicals were reagent grade; solvents were dried and distilled prior to use.

Ethyl 3-(2-ethyl-1,3-dioxolan-2-yl)propanoate **2b** was prepared by standard acetalization procedure from ethyl 4-oxohexanoate.[17,18]

3.1. 2-Alkyl-1-[2-(2-alkyl-1,3-dioxolan-2-yl)ethyl]-1-cyclopropanols (3a–c). General procedure

A solution of propyl- or butylmagnesium bromide (35 mmol) in a mixture of THF (8 mL) and diethyl ether (10 mL) was slowly added to a stirred solution of 10 mmol of corresponding ethyl 3-(2-alkyl-1,3-dioxolan-2-yl)-propanoate **2a**,**b** and Ti(O*i*-Pr)$_4$ (0.6 mL, 2 mmol) in THF (12 mL) at room temperature. The mixture was stirred for 2 h, treated with saturated solution of ammonium chloride,

filtered and extracted with ether (3×20 mL). Etheral extracts were washed with brine and dried (Na_2SO_4). The products were isolated by distillation under reduced pressure.

3.1.1. 2-Ethyl-1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1-cyclopropanol (3a). Yield: 1.8 g (90%); colourless liquid; bp 93–95 °C/1 Torr. IR (CCl_4): ν 3440, 3066, 2907, 2840, 1440, 1373, 1200, 1053 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.03 (t, J=5.2 Hz, 1H); 0.73 (dd, J=9.6, 5.2 Hz, 1H); 0.82–0.92 (m, 1H); 0.93 (t, J=7.2 Hz, 3H); 0.99–1.12 (m, 1H); 1.32 (s, 3H); 1.33–1.45 (m, 1H); 1.52–1.62 (m, 1H); 1.64–1.76 (m, 1H); 1.89 (t, J=7.4 Hz, 2H); 3.45 (br. s, 1H); 3.88–3.96 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.9, 19.1, 22.7, 23.5, 27.6, 28.3, 35.6, 58.6, 64.42, 64.45, 110.1. Anal. calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.77; H, 9.87.

3.1.2. 1-[2-(2-Ethyl-1,3-dioxolan-2-yl)ethyl]-2-methyl-1-cyclopropanol (3b). Yield: 1.56 g (78%); colourless liquid; bp 107–109 °C/3 Torr. IR (CCl_4): ν 3451, 3076, 2912, 2853, 1438, 1363, 1219, 1048 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.04–0.02 (m, 1H); 0.75–0.82 (m, 1H); 0.85–0.94 (m, 4H); 1.01 (s, 3H); 1.60–1.70 (m, 4H); 1.85–1.91 (m, 2H); 2.93 (br. s, 1H) 3.9–3.98 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 8.0, 14.1, 19.6, 20.6, 28.0, 29.6, 33.0, 58.5, 64.8, 64.9, 112.1. Anal. calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.11; H, 9.89.

3.1.3. 2-Methyl-1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-1-cyclopropanol (3c). Yield: 1.48 g (80%); colourless liquid; bp 92–93 °C/2 Torr. IR (CCl_4): ν 3467, 3053, 2947, 2893, 1467, 1387, 1053 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ −0.05–0 (m, 1H); 0.74–0.8 (m, 1H); 0.88 (dd, J=6.8, 2.0 Hz, 1H); 0.99 (d, J=1.6 Hz, 3H); 1.33 (s, 3H); 1.61–1.67 (m, 2H); 1.87–1.93 (m, 2H); 2.92 (br. s, 1H); 3.93–3.97 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.1, 19.5, 20.5, 23.6, 28.2, 35.6, 58.4, 64.4, 64.5, 110.1. Anal. calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.56; H, 9.57.

3.2. *trans*-3-(2-Alkyl-1,3-dioxolan-2-yl)-1-(3-alkyl-2-oxiranyl)-1-propanones (4a,b). General procedure

A solution of corresponding cyclopropanol **3a**,**c** (10 mmol) and Mn(II) abietate (0.1 g, 1 mol%) in dry benzene (60 mL) was stirred under oxygen atmosphere at room temperature for 3–5 h. Then aq KOH (0.5 M, 5 mL) was added and the mixture was vigorously stirred at room temperature for 1–2 h. After filtration, the organic layer was separated and the aqueous solution was extracted with benzene (3×5 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was removed and the crude epoxides **3a**–**g** were purified by distillation under reduced pressure.

3.2.1. *trans*-1-(3-Ethyl-2-oxiranyl)-3-(2-methyl-1,3-dioxolan-2-yl)-1-propanone (4a). Yield: 1.82 g (85%); colourless liquid; bp 93–95 °C/1 Torr. IR (film): ν 2977, 2881, 1711, 1436, 1378, 1223, 1131, 1053, 949, 920, 858 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J=7.6 Hz, 3H); 1.28 (s, 3H); 1.57–1.71 (m, 2H); 1.89–2.03 (m, 2H); 2.33 (ddd, J=17.4, 8.2, 6.4 Hz, 1H); 2.50 (ddd, J=17.4, 8.3, 6.4 Hz, 1H); 3.03 (td, J=5.3, 1.6 Hz, 1H); 3.21 (d, J=1.6 Hz, 1H); 3.85–3.94 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 9.4, 23.8, 24.8, 31.6, 32.3, 59.3, 64.55, 64.61, 109.0, 128.2, 207.1. Anal. calcd for $C_{10}H_{18}O_3$: C, 61.66; H, 8.47. Found: C, 61.84; H, 8.29.

3.2.2. *trans*-3-(2-Ethyl-1,3-dioxolan-2-yl)-1-(3-methyl-2-oxiranyl)-1-propanone (4b). Yield: 1.63 g (76%); colourless liquid; bp 115–117 °C/4 Torr. IR (film): ν 2970, 2883, 1714, 1464, 1422, 1306, 1204, 1141, 1067, 950, 897, 842, 769 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, J=7.6 Hz, 3H); 1.36 (d, J=4.8 Hz, 3H); 1.57 (q, J=7.6 Hz, 2H); 1.84–1.98 (m, 2H); 2.28 (ddd, J=17.6, 8.4, 6.4 Hz, 1H); 2.45 (ddd, J=17.6, 8.2, 6.8 Hz, 1H); 3.1 (qd, J=4.8, 1.6 Hz, 1H); 3.15 (d, J=1.6 Hz, 1H); 3.88 (s, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 7.9, 17.4, 29.8, 29.9, 31.6, 54.1, 60.5, 64.8, 64.9, 111.0, 207.1. Anal. calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.68; H, 8.41.

3.2.3. Preparation of 3-(2-methyl-1,3-dioxolan-2-yl)-1-(2-methyl-2-oxiranyl)-1-propanone (4c). Bromine–pyridine complex (2.38 g, 10 mmol) was added slowly to a stirred solution of cyclopropanol **3c** (1.86 g, 10 mmol) in dry Et_2O (25 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, filtered through a short pad of alumina and the solvent was evaporated. The residue was dissolved in pentane (30 mL) and stirred with Al_2O_3 (10 g) for 12 h. The reaction mixture was filtered, Al_2O_3 was washed with ether and the solvent was evaporated to give 2-methyl-5-(2-methyl-1,3-dioxolan-2-yl)-1-penten-3-one (**5**). This compound **5** was used for further transformations without purification (purity >95%; ^1H NMR spectroscopy). Yield: 1.73 g (94%); colourless liquid. IR (CCl_4): ν 3093, 2933, 2867, 1680, 1440, 1373, 1320, 1053, 933 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 3H); 1.85 (s, 3H); 1.99 (t, J=7.8 Hz, 2H); 2.76 (t, J=7.8 Hz, 2H); 3.86–3.97 (m, 4H); 5.74 (s, 1H); 5.95 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 17.7, 23.9, 32.0, 33.34, 64.6, 109.4, 124.2, 128.4. (The signal due to carbonyl group is not observed in the 200 ppm region). Anal. calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.01; H, 8.52.

To a stirred solution of this material (1.73 g, 9.4 mmol) and NaOH (0.5 g) in a mixture of *i*PrOH (12 mL) and H_2O (7 mL) was added 30% H_2O_2 (5 mL, 50 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, diluted with brine (25 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was removed and the crude epoxide **4c** was purified by column chromatography (silica gel, EtOAc–cyclohexane, 1:5). Yield: 1.5 g (80%); colourless liquid. IR (CCl_4): ν 2920, 2853, 1707, 1440, 1373, 1133, 1053 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (s, 3H); 1.48 (s, 3H); 1.86–2.02 (m, 2H); 2.25 (ddd, J=17.6, 8.4, 6.4 Hz, 1H); 2.51 (ddd, J=17.6, 8.5, 6.4 Hz, 1H); 2.82 (d, J=5.2 Hz, 1H); 2.96 (d, J=5.2 Hz, 1H); 3.86–3.96 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 16.6, 23.8, 29.5, 32.5, 51.9, 59.5, 64.46, 64.55, 109.1, 208.9. Anal. calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 60.11; H, 8.19.

3.3. 1-(2-Oxiranyl)-1,4-alkanediones (6a–c). General procedure

To a stirred suspension of silica gel (18 g) in CH_2Cl_2

(50 mL) was added 15% H_2SO_4 (1.7 g) followed by protected compound **4a–c** (10 mmol). The resulting mixture was allowed to stir at room temperature for 5–7 h, filtered and the solvent was evaporated, affording the crude diketones **6a–c** which were purified by column chromatography (silica gel, EtOAc–cyclohexane, 1:5).

3.3.1. *trans*-1-(3-Ethyl-2-oxiranyl)-1,4-pentanedione (6a). Yield: 1.63 g (96%); colourless liquid. IR (film): ν 2972, 2923, 2881, 1712, 1465, 1431, 1403, 1362, 1233, 1163, 1103, 919, 861 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, J=7.6 Hz, 3H); 1.53–1.74 (m, 2H); 2.12 (s, 3H); 2.49 (ddd, J=18.4, 7.0, 5.0 Hz, 1H); 2.54–2.60 (m, 1H); 2.60–2.66 (m, 1H); 2.76 (ddd, J=18.4, 7.8, 5.2 Hz, 1H); 3.13 (td, J=5.3, 2.0 Hz, 1H); 3.20 (d, J=2.0 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 9.3, 24.7, 29.6, 30.6, 36.2, 59.2, 59.3, 206.3, 206.4. Anal. calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.29; H, 8.15.

3.3.2. *trans*-1-(3-Methyl-2-oxiranyl)-1,4-hexanedione (6b). Yield: 1.53 g (90%); colourless liquid. IR (film): ν 2976, 2939, 1714, 1462, 1421, 1360, 1235, 1115, 1043, 1008, 973, 844 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, J=7.2 Hz, 3H); 1.39 (d, J=5.2 Hz, 3H); 2.45 (q, J=7.2 Hz, 2H); 2.48–2.68 (m, 3H); 2.73–2.83 (m, 1H); 3.18 (d, J=1.6 Hz, 1H); 3.27 (qd, J=5.2, 1.6 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 7.7, 17.5, 30.7, 35.0, 35.7, 54.4, 60.6, 206.4, 209.4. Anal. calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.73; H, 8.16.

3.3.3. 1-(2-Methyl-2-oxiranyl)-1,4-pentanedione (6c). Yield: 1.48 g (95%); colourless liquid. IR (CCl_4): ν 2973, 2907, 1707, 1387, 1160, 1067, 960, 920 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 3H); 2.17 (s, 3H); 2.45–2.54 (m, 1H); 2.56–2.67 (m, 2H) 2.77–2.85 (m, 1H); 2.86 (d, J=5.2 Hz, 1H); 3.14 (d, J=5.2 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 16.4, 29.1, 29.7, 36.5, 52.3, 59.5, 206.7, 208.1. Anal. calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.73; H, 7.55.

3.4. 6,8-Dioxabicyclo[3.2.1]octan-2-ones (7a–c). General procedure

To a stirred solution of 1-(2-oxiranyl)-1,4-alkanedione **6a–c** (10 mmol) in CH_2Cl_2 (240 mL) was added $BF_3{\cdot}OEt_2$ (0.42 g, 3.3 mmol). The reaction mixture was stirred at room temperature for 4–5 h, treated with aqueous 10% NaOH (20 mL) and extracted with CH_2Cl_2 (3×10 mL). The extracts were dried (Na_2SO_4) and the solvent was removed. Compounds **7a–c** were isolated by distillation under reduced pressure or by recristallization.

3.4.1. *endo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]-octan-2-one (7a).[14] Yield: 1.45 g (85%); colourless liquid; bp 87–88 °C/10 Torr. IR (film): ν 2970, 2940, 2880, 1729, 1448, 1384, 1225, 1200, 1172, 1084, 1040, 969, 896, 853 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, J=7.4 Hz, 3H); 1.38 (dquint, J=14.4, 7.2 Hz, 1H); 1.47–1.61 (m, 1H); 1.54 (s, 3H); 2.01–2.10 (m, 2H); 2.32 (td, J=18.4, 8.4 Hz, 1H); 2.44 (ddd, J=18.4, 7.6, 4.0 Hz, 1H); 3.98 (td, J=7.2, 4.8 Hz, 1H); 4.26 (d, J=4.8 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.3, 22.5, 24.2, 33.3, 34.2, 80.1, 83.3, 107.4, 205.3. Anal. calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.32; H, 8.39.

3.4.2. *endo*-5-Ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]-octan-2-one (7b). Yield: 1.33 g (78%); colourless liquid; bp 94–96 °C/14 Torr. IR (CCl_4): ν 2995, 2947, 2880, 1735, 1493, 1467, 1387, 1200, 1120, 1080, 933 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J=7.4 Hz, 3H); 1.14 (d, J=6.4 Hz, 3H); 1.78 (qd, J=7.4, 2.4 Hz, 2H); 1.9–2.07 (m, 2H); 2.30 (td, J=18.4, 8.0 Hz, 1H); 2.46 (ddd, J=18.4, 8.4, 3.2 Hz, 1H); 4.13 (qd, J=6.0, 4.8 Hz, 1H); 4.18 (d, J=4.8 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 7.2, 14.1, 30.2, 32.6, 33.4, 74.4, 83.9, 109.1, 206.0. MS (70 eV) m/z (%): 170 (0.2), 149 (5), 116 (1), 113 (2), 87 (1), 86 (2), 75 (4), 74 (100), 73 (1), 72 (1), 71 (1), 70 (1), 69 (2), 60 (23), 58 (2), 57 (13), 56 (63), 55 (4), 54 (2), 46 (7), 45 (66), 44 (14), 43 (57), 42 (24), 41 (11), 40 (2), 39 (2). Anal. calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.64; H, 8.19.

3.4.3. 1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octan-2-one (7c).[15] Yield: 1.07 g (69%); mp 53–54 °C (hexane) [Lit.[12] mp 52.7–53.4 °C (hexane/Et_2O)]. IR (CCl_4): ν 2933, 2867, 1734, 1453, 1373, 1200, 1187, 1053, 960 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 1H); 1.53 (s, 1H); 2.13 (dd, J=8.8, 5.6 Hz, 2H); 2.36–2.57 (m, 2H); 3.55 (d, J=8.0 Hz, 1H); 3.91 (d, J=8.0 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.1, 23.9, 32.6, 36.6, 72.9, 84.6, 108.1, 206.4. Anal. calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.40; H, 7.61.

3.5. Preparation of (±)-*endo*-brevicomin (1b), (±)-*endo*-isobrevicomin (1d) and (±)-frontalin (1e)

3.5.1. (±)-*endo*-Isobrevicomin (1d). To a stirred solution of ketone **7b** (0.34 g, 2 mmol) and 1,2-ethanedithiol (0.2 mL, 2.4 mmol) in CH_2Cl_2 (10 mL) was slowly added a solution of $BF_3{\cdot}Et_2O$ (0.43 g, 3 mmol) in CH_2Cl_2 (5 mL) at −5 °C. The reaction mixture was stirred at −5–0 °C for 12–14 h, treated with aqueous 10% NaOH (10 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined extracts were dried (Na_2SO_4) and concetrated in vacuo. Column chromatography (SiO_2, benzene) of the residue gave the ethylene thioketal of ketone **7b**. Yield: 0.30 g (61%); colourless liquid. ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J=7.4 Hz, 3H); 1.48 (d, J=6.4 Hz, 3H); 1.67–1.77 (m, 3H); 1.91 (ddd, J=13.6, 11.6, 5.2 Hz 1H); 2.05 (ddt, J=1.6, 5.6, 13.6 Hz, 1H); 2.47 (ddd, J=14.0, 11.6, 6.0 Hz, 1H); 3.04 (ddd, J=11.5, 9.2, 4.7 Hz, 1H); 3.17–3.31 (m, 2H), 3.44 (dt, J=10.9, 4.6 Hz 1H), 4.18–4.26 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 6.9, 15.2, 30.0, 34.3, 36.4, 36.6, 40.9, 67.6, 76.1, 85.3, 108.3.

A solution of ethylene thioketal of ketone **7b** (246 mg, 1 mmol) in EtOH (30 mL) was refluxed for 4 h with W2 Raney nickel (5 g). After cooling the catalyst was removed by filtration. The filtrate was concentrated under atmospheric pressure and (±)-*endo*-isobrevicomin (**1d**) was isolated by column chromatography (pentane–Et_2O, 19:1). Yield: 131 mg (84%); colourless liquid. All spectral data were identical with those reported for **1d**.[3,7e]

3.5.2. (±)-*endo*-Brevicomin (1b). Ethylene thioketal of ketone **7a**[14] was prepared from **7a** (0.34 g, 2 mmol) in the same manner as described above. Yield: 0.26 g (53%);

colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (t, J=7.4 Hz, 3H); 1.45 (s, 3H); 1.69–2.05 (m, 5H); 2.45 (ddd, J=13.5, 11.6, 6.0 Hz, 1H); 3.03 (ddd, J=11.3, 9.5, 4.8 Hz, 1H); 3.17–3.31 (m, 2H); 3.40 (dt, J=10.9, 4.5 Hz, 1H); 4.01 (ddd, J=8.8, 5.0, 3.9 Hz, 1H); 4.22 (dd, J=3.9, 1.6 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.9, 22.7, 24.1, 35.9, 36.4, 36.5, 40.7, 67.5, 82.1, 85.0, 106.4.

This material (246 mg, 1 mmol) was converted to (±)-*endo*-brevicomin (**1b**) in 80% yield.[14] All spectral data were identical with those reported for **1b**.[2g,6d,14]

3.5.3. (±)-Frontalin (1e). Ethylene thioketal of ketone **7c**[15] was prepared from **7c** (0.31 g, 2 mmol) in the same manner as described above. Yield: 0.44 g (95%); colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 3H); 1.59 (s, 3H); 1.79 (dd, J=13.2, 5.4 Hz, 1H); 1.90 (td, J=12.8, 5.4 Hz, 1H); 2.11 (dd, J=14.2, 5.0 Hz, 1H); 2.33–2.43 (m, 1H); 3.11–3.24 (m, 2H); 3.28–3.4 (m, 2H); 3.62 (d, J=8.0 Hz, 1H); 4.05 (d, J=8.0 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.1, 23.9, 36.8, 38.1, 39.3, 40.2, 71.8, 74.4, 86.9, 108.3.

This material was converted to (±)-frontalin (**1e**) in 72% yield.[12] All spectral data were identical with those reported for **1e**.[4b,c]

3.6. Preparation of hydroxy compounds 8a, 9a and their derivatives 8b, 9b

3.6.1. (1*R* *,2*S* *,5*S* *,7*S* *)-*endo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octan-2-ol (8a). To a stirred suspension of $LiAlH_4$ (0.06 g, 1.4 mmol) in Et_2O (3 mL) was slowly added a solution of ketone **7a** (0.34 g, 2 mmol) in Et_2O (2 mL). The reaction mixture was stirred for 2 h, treated with 5% HCl (about 4 mL) until pH=7.5 and extracted with Et_2O (3×5 mL). The organic extracts were dried (Na_2SO_4) and filtered through a short pad of silica gel to provide, after concentration, alcohol **8a** (purity>95%; ^{1}H NMR spectroscopy). Yield: 0.33 g (96%); colourless liquid. IR (CCl_4): ν 3480, 2994, 2947, 2880, 1480, 1401, 1267, 1213, 1186, 1093, 1053, 1020, 920, 893, 867 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ 1.12 (t, J=7.4 Hz, 3H); 1.56 (s, 3H); 1.59–1.78 (m, 4H); 1.91–2.19 (m, 2H); 3.81–3.91 (m, 1H); 4.01 (t, J≈4.4 Hz, 1H); 4.12–4.20 (m, 1H). ^{13}C NMR (100.6 MHz, C_6D_6): δ 11.9, 22.1, 24.4, 27.3, 35.4, 68.7, 78.2, 82.9, 106.6. MS (70 eV) *m*/*z* (%): 172 (0.6), 143 (1), 115 (4), 114 (19), 113 (1), 112 (2), 102 (1), 101 (6), 99 (3), 97 (4), 96 (1), 95 (3), 87 (1), 86 (9), 85 (12), 84 (21), (83 (21), 81 (5), 79 (1), 74 (1), 73 (20), 72 (12), 71 (23), 70 (6), 69 (7), 68 (1), 67 (4), 61 (18), 60 (2), 59 (11), 58 (25), 57 (24), 56 (21), 55 (26), 54 (4), 53 (4), 45 (5), 44 (5), 43 (100), 42 (6), 41 (22), 40 (2), 39 (15). Anal. calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.51; H, 9.23.

3.6.2. (1*R* *,2*S* *,5*S* *,7*S* *)-*endo*-7-Ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]oct-2-yl methanesulfonate (8b). To a stirred solution of NaH (50% in oil) (192 mg, 4 mmol) and imidazole (2.5 mg) in THF (5 mL) was added alcohol **8a** (172 mg, 1 mmol). The reaction mixture was stirred at room temperature for 1 h and MsCl (0.4 mL, 5 mmol) was added. The resulting mixture was stirred for 7 h, treated with saturated $NaHCO_3$ (10 mL) and extracted with ether (3×5 mL). The organic extract was dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by recrystallization (hexane–Et_2O, 10:1). Yield: 150 mg (60%); mp 61.5–62.5 °C (hexane–Et_2O). IR (CCl_4): ν 2973, 2933, 2880, 1373, 1347, 1187, 960, 920, 867, 733 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, J=7.2 Hz, 3H); 1.44 (s, 3H); 1.74–1.95 (m, 4H); 2.00–2.08 (m, 1H); 2.22 (qd, J=10.9, 6.8 Hz, 1H); 3.02 (s, 3H); 4.08 (td, J=7.3, 3.9 Hz, 1H); 4.34 (t, J≈4.0 Hz, 1H); 4.88 (ddd, J=10.9, 6.2, 4.4 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.3, 21.4, 23.7, 24.6, 35.2, 38.3, 75.8, 75.9, 82.3, 106.8.

3.6.3. (1*R* *,3*S* *,4*S* *,5*S* *)-3-Ethyl-1-methyl-2,8-dioxabicyclo[3.2.1]octan-4-ol (9a).[3] A solution of alcohol **8a** (172 mg, 1 mmol) and TsOH (8.6 mg, 0.05 mmol) in ether (3 mL) was kept for 3 h at room temperature. The solvent was evaporated and the residue was recrystallized. Yield: 138 mg (80%); mp 64–65 °C (hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, J=7.4 Hz, 3H); 1.46 (s, 3H); 1.39–1.51 (m, 1H); 1.69–2.10 (m, 5H); 2.35 (br. s, 1H); 3.30 (td, J=8.4, 2.7 Hz, 1H); 3.47 (dd, J=8.4, 4.2 Hz, 1H); 4.27 (dd, J=6.4, 4.2 Hz, 1H). ^{1}H NMR (400 MHz, C_6D_6): δ 0.92 (br.s, 1H); 1.04 (t, J=7.4 Hz, 3H); 1.52 (s, 3H); 1.45–1.55 (m, 2H); 1.57–1.67 (m, 1H); 1.69–1.80 (m, 2H); 1.88 (ddd, J=12.0, 9.3, 4.0 Hz, 1H); 3.22 (td, J=8.3, 2.3 Hz, 1H); 3.25–3.31 (m, 1H); 4.08 (dd, J=6.8, 3.8 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 9.5, 23.4, 23.6, 25.3, 33.8, 68.0, 74.9, 78.1, 105.3. ^{13}C NMR (100.6 MHz, C_6D_6): δ 9.9, 23.91, 23.93, 26.0, 34.3, 68.6, 75.2, 78.3, 105.3.

3.6.4. (1*S* *,2*S* *,3*S* *,5*R* *)-3-Ethyl-5-methyl-4,8-dioxabicyclo[3.2.1]oct-2-yl methanesulfonate (9b). To a stirred solution of alcohol **9a** (0.34 g, 2 mmol) and Et_3N (0.56 mL, 4 mmol) in ether (7 mL) was added MsCl (0.35 g, 3 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h, treated with saturated $NaHCO_3$ (10 mL) and extracted with ether (3×5 mL). The organic extract was dried (Na_2SO_4) and solvent was evaporated. The crude product was purified by recristallization (hexane). Yield: 0.45 g (90%); mp 73–74 °C (hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J=7.4 Hz, 3H); 1.48 (s, 3H); 1.43–1.56 (m, 1H); 1.67–1.79 (m, 1H); 1.82–1.94 (m, 1H); 1.99–2.10 (m, 3H); 3.02 (s, 3H); 3.51 (td, J=8.9, 2.8 Hz, 1H); 4.39 (dd, J=8.9, 4.3 Hz, 1H); 4.60 (dd, J=6.2, 4.3 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 9.0, 23.1, 24.0, 24.9, 33.5, 38.3, 71.5, 74.9, 75.9, 105.8.

Methanesulfonate **9b** could also be obtained from alcohol **8a** (0.34 g, 2 mmol) in the same manner as from **9a**. Yield: 0.45 g (90%).

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