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Enantiodivergent synthesis of both antipodes of hydroxy-*exo*-brevicomin from L-(+)-tartaric acid

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Abstract—An enantiodivergent approach to both antipodes of hydroxy-*exo*-brevicomin was achieved from a common chiral precursor L-(+)-tartaric acid. The strategy utilizes the elaboration of a keto-Weinreb amide and successive stereoselective reductions.

1. Introduction

Alkylated 6,8-dioxabicyclo[3.2.1]octane structural units are widespread in bioactive natural products. These compounds can have simple bicyclic structures such as the pine beetle pheromones or can be very complex systems that originate from marine sources. Brevicomin **1** and frontalin **2** were the first pheromones to be identified belonging to the 6,8-dioxabicyclo[3.2.1]octane.[1] Similar structures having varied bicyclooctane structures such as multistriatin **3** and *iso-exo*-brevicomin **4** were isolated in addition to a number of other compounds from different *Dendroctonus* species. Marine tunicates belonging to the genus *Didemnum* produce serinolipids such as didemniserinolipid B **6**, which possess the same bicyclic core.[2] Francke et al. reported the isolation and synthesis of hydroxy-*exo*-brevicomin **5**, 1-(5-methyl-6,8-dioxabicyclo[3.2.1]oct-7-yl)ethanol from the head-space extracts of *Dendroctonus ponderosae* (Fig. 1).[3] These pheromones play a crucial role in the communication system of these beetle species and their enantioselective synthesis is highly desirable in the study of structure–activity relationships and in pest management.[4] Recently we have accomplished a concise enantiospecific synthesis of hydroxy-*exo*-brevicomin from natural L-(+)-tartaric acid.[5] Herein, we report the full details delineating the synthesis of hydroxy-*exo*-brevicomin[6] including an efficient enantiodivergent approach for the access of both antipodes of the title compound starting from the same chiral entity, i.e., L-(+)-tartaric acid.

It was anticipated that the precursor triols **17** and *ent*-**17** for the synthesis of both antipodes of hydroxy-*exo*-brevicomin **5** can be accessed by elaboration of keto-Weinreb amides **8** and **9**, respectively. Synthesis of amides **8** and **9** can be accomplished by a controlled addition of the corresponding Grignard reagent to the bis-Weinreb amide **7** derived from tartaric acid (Scheme 1).

Thus, addition of 4-pentenylmagnesium bromide or MeMgBr to the bis-Weinreb amide[7] **7** afforded the keto amides **8** or **9** in 92 and 60% yields, respectively. The keto group in **8** and **9** was reduced with L-Selectride, yielding a single diastereomer of the alcohols,[8] which were subsequently

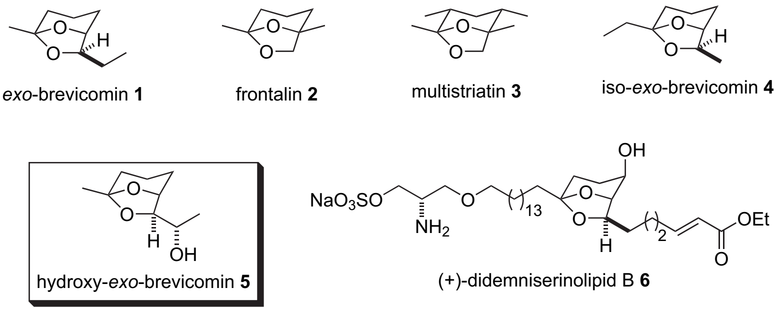

Figure 1. Bio-active bicyclic acetals possessing 6,8-dioxabicyclo[3.2.1]octane skeleton.

Keywords: Stereoselective reduction; L-(+)-Tartaric acid; Hydroxy-*exo*-brevicomin; 6,8-Dioxabicyclo[3.2.1]octane.

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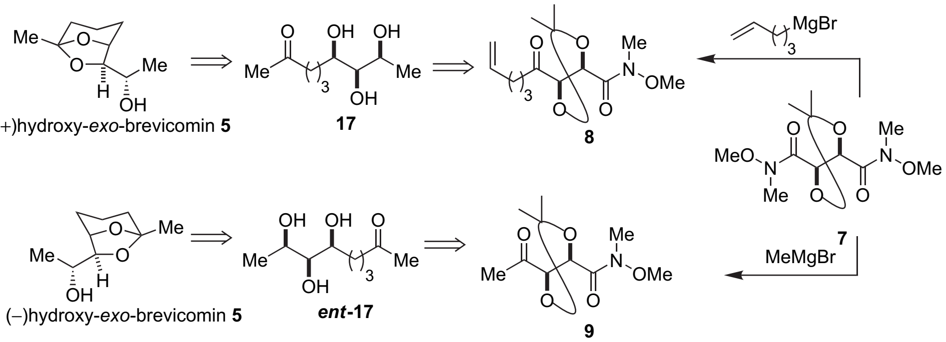
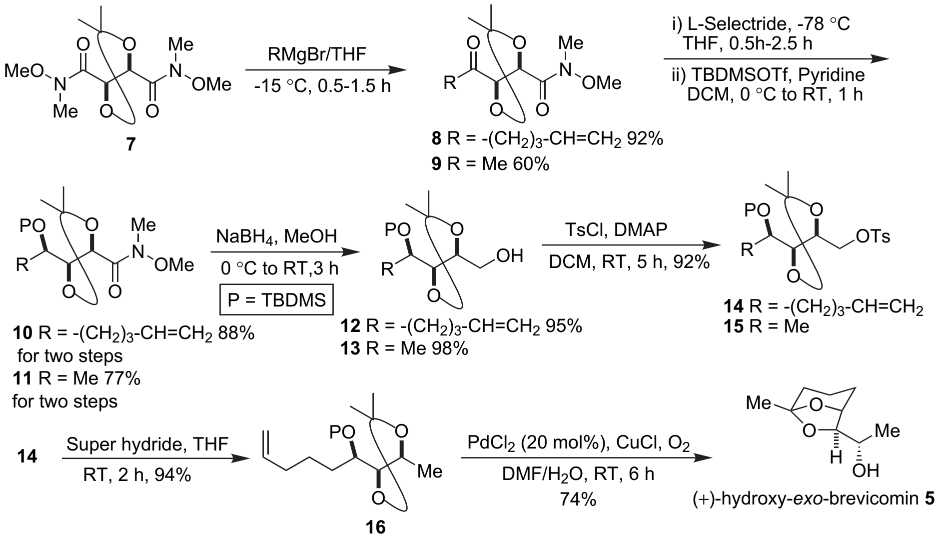


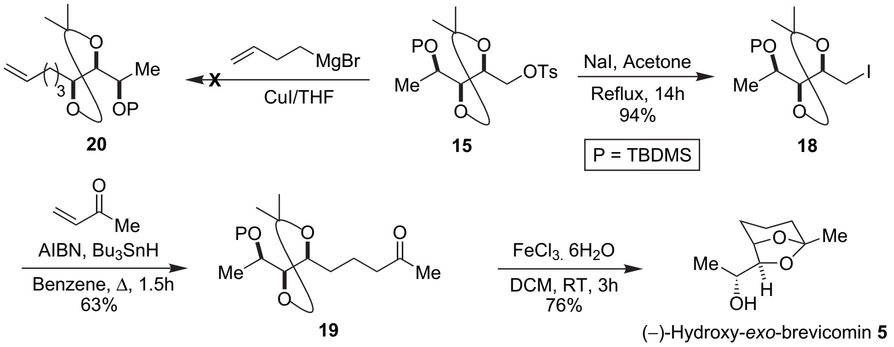
Scheme 1. Retrosynthesis for (+)- and (−)-hydroxy-*exo*-brevicomin from L-(+)-tartaric acid.



Scheme 2. Synthesis of (+)-hydroxy-*exo*-brevicomin.

protected as their silyl ethers **10** and **11**. High reactivity of the Weinreb amide in **10** and **11** was then exploited and the reduction of **10** and **11** with $NaBH_4$ resulted in alcohols **12** and **13**, respectively. Alcohols **12** and **13** were converted using standard conditions into the corresponding tosylates **14** and **15**, pivotal precursors for the access of triols **17** and *ent*-**17** (Scheme 2). Reduction of the tosylate **14** with superhydride[9] produced **16**, which under Wacker oxidation[10] conditions, produced (+)-hydroxy-*exo*-brevicomin ($[\alpha]_D^{25}$ +61.2 (*c* 2.4, $CHCl_3$), lit.[6a] $[\alpha]_D^{25}$ +61.3 (*c* 1.18, $CHCl_3$)), via the formation of the trihydroxy ketone **17**. The synthetic sample exhibited spectral data identical to that of an authentic sample.

The synthesis of *ent*-**17**, the precursor for (−)-hydroxy-*exo*-brevicomin, was envisaged by the coupling of the tosylate **15** with 3-butenylmagnesium bromide in the presence of CuI followed by transformation of alkene into *ent*-**17** under Wacker oxidation conditions. Efforts for the displacement of the tosylate **15** with the Grignard reagent under various conditions failed to yield the alkene **20**. To circumvent this problem, tosylate **15** was converted into the iodide **18**, which on Bu_3SnH/AIBN mediated radical addition[11] to methyl-vinyl ketone produced the ketone **19** in 63% yield (71% based on starting material consumption). Simultaneous deprotection of the silyl group and the acetonide[12] was achieved in a single pot with $FeCl_3$ yielding *ent*-**17**, which under the conditions spontaneously underwent ketalization to produce (−)-hydroxy-*exo*-brevicomin $[\alpha]_D^{25}$ −62.5 (*c* 0.8, $CHCl_3$). Spectral data are identical to that of the (+)-isomer prepared (vide supra).



In summary, an enantiodivergent approach to both antipodes of hydroxy-*exo*-brevicomin was accomplished starting from a single chiral entity, i.e., L-(+)-tartaric acid. (+)- and (−)-hydroxy-*exo*-brevicomin were prepared in 48 and 20% overall yields starting from the bis-Weinreb amide derived from L-(+)-tartaric acid. The synthetic transformations are simple, highly selective, and are applicable for the synthesis of a number of oxygen containing heterocycles.

2. Experimental

2.1. General

Column chromatography was performed on silica gel, Acme grade 100–200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were uncorrected. Unless stated otherwise, all the reactions were performed under inert atmosphere. Optical rotations were measured on a JASCO DIP-370 digital polarimeter at 25 °C.

2.1.1. Preparation of (4*R*,5*R*)-5-(hex-5-enoyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (8). In an oven dried two neck 50 mL round-bottom flask equipped with magnetic stirrer and argon inlet was placed the bis-Weinreb amide (**7**) (0.5 g, 1.8 mmol) dissolved in 6 mL of THF. This was cooled to −15 °C and a THF solution of 4-pentenylmagnesium bromide (3 mL, 1 M solution in THF, 3 mmol) was added dropwise under argon atmosphere. The reaction mixture was stirred for 0.5 h at the same temperature. After the reaction was complete (TLC), it was quenched with satd NH_4Cl (8 mL) and extracted with ether (3×10 mL). The combined ethereal extracts were washed with brine and dried (Na_2SO_4). The residue obtained after the evaporation of solvent was purified by column chromatography to yield **8** in 92% (0.47 g) as colorless oil. $[\alpha]_D$ +6.6 (*c* 1.8, $CHCl_3$); IR (neat): 2989, 1718, 1654, 1504, 1455, 1382, 1259, 1155, 1083, 997, 863, 804 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (ddt, J=17.1, 10.2, 6.6 Hz, 1H), 5.06–4.97 (m, 3H), 4.82 (d, J=5.4 Hz, 1H), 3.71 (s, 3H), 3.23 (s, 3H), 2.77–2.55 (m, 2H), 2.11–2.04 (m, 2H), 1.76–1.66 (m, 2H), 1.49 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 169.7, 137.7, 115.3, 112.7, 82.2, 73.9, 61.6, 38.4, 32.9, 32.5, 26.6, 26.2, 22.1; HRMS for $C_{14}H_{23}NO_5$+Na calcd 308.1474; found 308.1480.

2.1.2. Preparation of (4*R*,5*R*)-5-acetyl-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (9). In an oven dried two neck 50 mL round-bottom flask equipped with magnetic stirrer and argon inlet was placed the bis-Weinreb amide (7) (0.4 g, 1.5 mmol) dissolved in 6 mL of THF. This was cooled to −15 °C and a THF solution of methylmagnesium bromide (0.6 mL, 3 M solution in THF, 1.8 mmol) was added dropwise under argon atmosphere. The reaction was stirred for 0.5 h at the same temperature. After the reaction was complete (TLC), it was quenched with satd NH_4Cl (7 mL) and extracted with ether (3×10 mL). The combined ethereal extracts were washed with brine and dried (Na_2SO_4). The residue obtained after the evaporation of solvent was purified by column chromatography to yield **9** in 60% (0.2 g) as colorless oil. $[\alpha]_D$ +5.5 (*c* 5.6, $CHCl_3$); IR (neat): 2987, 2854, 1720, 1671, 1459, 1375, 1255, 1182, 1085, 997, 923, 852, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.04 (d, J=5.7 Hz, 1H), 4.83 (d, J=5.7 Hz, 1H), 3.73 (s, 3H), 3.24 (s, 3H), 2.31 (s, 3H), 1.50 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 169.3, 112.4, 82.3, 73.6, 61.3, 32.1, 26.3, 25.9; HRMS for $C_{10}H_{17}NO_5$+Na calcd 254.1004; found 254.1005.

2.1.3. Preparation of (4*R*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxyhex-5-enyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (10). To a solution of **8** (0.45 g, 1.5 mmol) in 4 mL of THF at −78 °C was added L-Selectride (3 mL, 1 M solution in THF, 3 mmol) dropwise over a period of 10 min, under argon atmosphere. The reaction mixture was stirred for 2.5 h at the same temperature, quenched with water (6 mL), and extracted with ether (3×10 mL). The combined ethereal extracts were washed with brine and dried over Na_2SO_4. Residue obtained after evaporation of solvent was subjected to column chromatography to afford (4*R*,5*S*)-5-((*R*)-1-hydroxyhex-5-enyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide as colorless oil in 89% (0.41 g) yield. $[\alpha]_D$ −5.5 (*c* 1.8, $CHCl_3$); IR (neat): 3465, 2984, 1670, 1451, 1381, 1259, 1161, 1065, 990, 879 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, J=17.0, 10.2, 6.6 Hz, 1H), 5.03–4.93 (m, 2H), 4.75 (br s, 1H), 4.36 (br s, 1H), 3.74 (s, 3H), 3.62–3.60 (m, 1H), 3.23 (s, 3H), 2.08–2.04 (m, 2H), 1.68–1.42 (m, 4H), 1.48 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 138.5, 114.7, 111.1, 80.7, 73.8, 70.2, 61.6, 38.4, 34.0, 33.5, 27.0, 26.1, 25.1.

To a solution of alcohol prepared above (0.4 g, 1.4 mmol) in 3 mL of CH_2Cl_2 and 1 mL of pyridine at 0 °C was added TBDMSOTf (0.4 mL, 1.6 mmol) under argon atmosphere. The reaction mixture was stirred for 1 h and allowed to warm up to room temperature. Progress of the reaction was monitored by TLC and after the reaction was complete, it was poured into water (6 mL) and extracted with ether (3×10 mL). The combined ethereal extracts were washed with brine and dried (Na_2SO_4). Evaporation of solvent followed by column chromatography of the resulting residue afforded **10** as colorless oil in 98% (0.55 g) yield. $[\alpha]_D$ −6.2 (*c* 1.3, $CHCl_3$); IR (neat): 2935, 2858, 1674, 1471, 1380, 1371, 1255, 1162, 1072, 993, 912, 836, 811, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.72 (ddt, J= 16.8, 10.2, 6.6 Hz, 1H), 5.10–4.75 (m, 2H), 4.63 (br s, 1H), 4.55–4.35 (m, 1H), 3.85–3.65 (m, 1H), 3.68 (s, 3H), 3.15 (s, 3H), 2.10–1.93 (m, 2H), 1.60–1.38 (m, 4H), 1.37 (s, 3H), 1.34 (s, 3H), 0.80 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 138.6, 114.5, 110.9, 80.2, 72.3, 72.0, 61.8, 33.7, 32.2, 26.9, 26.2, 26.1, 25.8, 24.9, 18.1, −4.5; HRMS for $C_{20}H_{39}NO_5Si$+Na calcd 424.2495; found 424.2462.

2.1.4. Preparation of (4*R*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (11). To a solution of **9** (0.15 g, 0.65 mmol) in 4 mL of THF at −78 °C was added L-Selectride (1.2 mL, 1 M solution in THF, 1.2 mmol) dropwise over 10 min, under argon atmosphere. The reaction mixture was stirred for 0.5 h, quenched with water (3 mL) and extracted with ether (3×6 mL). The combined ethereal extracts were washed with brine and dried over Na_2SO_4. Residue obtained after evaporation of solvent was filtered through silica and evaporated to yield crude alcohol. Using a similar procedure described for the synthesis of **10**, the alcohol was converted to the silylether **11**. Alternately, the same reaction can be effected using TBDMSCl as described below.

To a solution of crude alcohol (obtained above) in 3 mL of DMF at room temperature were added imidazole (0.09 g, 1.38 mmol), DMAP (10 mg, 0.07 mmol), and TBDMSCl (0.21 g, 1.38 mmol) and was heated up to 80 °C. The reaction mixture was stirred for 2 h at same temperature. After the reaction was complete (TLC), it was cooled to room temperature, poured into water (5 mL) and extracted with ether (3×10 mL). The combined ethereal extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the resulting residue afforded **11** as colorless oil in 77% (0.17 g) yield. $[\alpha]_D$ −16 (*c* 2.3, $CHCl_3$); IR (neat): 2954, 2896, 1673, 1463, 1380, 1255, 1159, 1074, 1008, 979, 894, 836, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (br s, 1H), 4.50 (dd, *J*=6.6, 4.5 Hz, 1H), 4.03 (qd, *J*=6.3, 4.5 Hz, 1H), 3.75 (s, 3H), 3.22 (s, 3H), 1.45 (s, 6H), 1.19 (d, *J*=6.3 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 111.1, 81.2, 72.2, 67.7, 61.7, 32.2, 27.0, 26.3, 25.7, 18.7, 18.0, −4.5, −4.9; HRMS for $C_{16}H_{33}NO_5Si$+Na calcd 370.2026; found 370.2021.

2.1.5. Preparation of (4*S*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxyhex-5-enyl)-4-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane (12). To a solution of **10** (0.33 g, 0.82 mmol) in 3 mL of methanol at 0 °C was added $NaBH_4$ (0.078 g, 2.1 mmol) in portion wise. The reaction mixture was stirred for 1 h at the same temperature and slowly warmed up to room temperature and stirred at room temperature for 2 h. After the reaction was complete (indicated by TLC), it was poured into water (5 mL) and extracted with ether (3×10 mL). Combined ethereal extracts were washed with brine and dried over Na_2SO_4. Residue obtained after evaporation of solvent was purified by column chromatography to yield **12** in 95% (0.27 g) as colorless oil. $[\alpha]_D$ +12.1 (*c* 2.4, $CHCl_3$); IR (neat): 3469, 2985, 2857, 1471, 1461, 1378, 1253, 1164, 1101, 1004, 937, 836, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (ddt, *J*=16.8, 10.2, 6.6 Hz, 1H), 4.94–4.84 (m, 2H), 3.93 (dt, *J*=8.1, 4.8 Hz, 1H), 3.77–3.55 (m, 4H), 2.37 (br s, 1H), 1.98–1.95 (m, 2H), 1.60–1.24 (m, 4H), 1.31 (s, 3H), 1.30 (s, 3H), 0.81 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 114.7, 108.6, 80.5, 77.0, 71.9, 62.9, 33.7, 31.9, 27.0, 26.9, 25.8, 25.3, 18.1, −4.2, −4.7; HRMS for $C_{18}H_{36}O_4Si$+Na calcd 367.2281; found 367.2281.

2.1.6. Preparation of (4*S*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-4-(hydroxylmethyl)-2,2-dimethyl-1,3-dioxolane (13). To a solution of **11** (0.15 g, 0.43 mmol) in 3 mL of methanol at 0 °C was added $NaBH_4$ (0.04 g, 1 mmol) in portions. The reaction mixture was stirred for 1 h at the same temperature and was slowly warmed up to room temperature and stirred for 1 h. After the reaction was complete (TLC), it was poured into water (5 mL) and extracted with ether (3×5 mL). Combined ethereal extracts were washed with brine and dried over Na_2SO_4. Residue obtained after evaporation of solvent was purified by column chromatography to yield **13** in 98% (0.12 g) as colorless oil. $[\alpha]_D$ +6.4 (*c* 2.8, $CHCl_3$); IR (neat): 3473, 2933, 2857, 1471, 1378, 1255, 1157, 1106, 835, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02–3.91 (m, 2H), 3.74–3.57 (m, 3H), 2.69 (t, *J*=6.6 Hz, 1H), 1.31 (s, 6H), 1.12 (d, *J*=6.6 Hz, 3H), 0.80 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.7, 81.4, 76.6, 67.7, 63.1, 27.1, 26.9, 25.7, 18.1, 18.0, −4.7, −4.9.

2.1.7. Preparation of (4*S*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxyhex-5-enyl)-4-(*p*-toluenesulfonyloxymethyl)-2,2-dimethyl-1,3-dioxolane (14). To a solution of **12** (0.25 g, 0.73 mmol) and DMAP (0.22 g, 1.8 mmol) in 5 mL of CH_2Cl_2 at 0 °C was added *p*-toluenesulfonyl chloride (0.21 g, 1.1 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for 5 h, poured into water (8 mL) and extracted with ether (3×10 mL). The ethereal extracts were washed with brine and dried over Na_2SO_4. Residue obtained after evaporation of solvent was subjected to column chromatography to yield **14** in 92% (0.33 g) as colorless oil. $[\alpha]_D$ −7.2 (*c* 1.1, $CHCl_3$); IR (neat): 2929, 2857, 1598, 1461, 1369, 1253, 1189, 1095, 983, 835, 775, 665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J*=8.4 Hz, 2H), 7.28 (d, *J*=8.4 Hz, 2H), 5.73 (ddt, *J*=16.8, 10.2, 6.6 Hz, 1H), 4.98–4.87 (m, 2H), 4.15 (dd, *J*=10.5, 3.0 Hz, 1H), 4.09–4.02 (m, 1H), 3.96 (dd, *J*=10.5, 5.7 Hz, 1H), 3.76–3.66 (m, 2H), 2.39 (s, 3H), 1.99–1.96 (m, 2H), 1.56–1.23 (m, 4H), 1.30 (s, 3H), 1.25 (s, 3H), 0.80 (s, 9H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 138.4, 132.8. 129.8. 128.0, 114.7, 109.7, 79.2, 74.4, 71.5, 70.0, 33.6, 32.0, 26.9, 26.8, 25.8, 25.0, 21.6, 18.0, −4.2, −4.6. HRMS for $C_{25}H_{42}O_6SSi$+Na calcd 521.2371; found 521.2369.

2.1.8. Preparation of (4*S*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-4-(*p*-toluenesulfonyloxymethyl)-2,2-dimethyl-1,3-dioxolane (15). To a solution of **13** (0.12 g, 0.41 mmol) and DMAP (0.12 g, 1 mmol) in 5 mL of CH_2Cl_2 at 0 °C was added *p*-toluenesulfonyl chloride (0.11 g, 0.6 mmol) under argon atmosphere. The reaction mixture was stirred at room temperature for 5 h, poured into water (5 mL), and extracted with ether (3×5 mL). The ethereal extracts were washed with brine and dried over Na_2SO_4. Residue obtained after evaporation of solvent was subjected to column chromatography to yield **15** in 92% (0.17 g) as colorless oil. $[\alpha]_D$ −19.1 (*c* 1.1, $CHCl_3$); IR (neat): 2931, 2857, 1598, 1461, 1369, 1255, 1178, 1097, 981, 835, 777, 665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J*=8.1 Hz, 2H), 7.33 (d, *J*=8.1 Hz, 2H), 4.21 (dd, *J*=10.2, 2.7 Hz, 1H), 4.16–3.90 (m, 3H), 3.74 (dd, *J*=7.5, 4.5 Hz, 1H), 2.43 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H), 1.12 (d, *J*=6.3 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 132.8, 129.7, 127.9, 109.8, 79.8, 74.1, 70.2, 67.3, 26.9, 26.8, 25.7, 21.6, 18.2, 17.9, −4.7, −4.9; HRMS for $C_{21}H_{36}O_6SSi$+Na calcd 467.1900; found 467.1877.

2.1.9. Preparation of (4*S*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxyhex-5-enyl)-4-methyl-2,2-dimethyl-1,3-dioxolane (16). To a solution of **14** (0.25 g, 0.5 mmol) in 3 mL of THF was added superhydride (2.5 mL, 1 M solution in THF, 2.5 mmol) dropwise at room temperature, under argon atmosphere. The reaction mixture was stirred at the same temperature for 2 h. After the reaction was complete (TLC), it was cautiously quenched with water (3 mL), and extracted with ether (3×5 mL). Combined ethereal extracts were washed with brine and dried (Na_2SO_4). Evaporation of solvent under reduced pressure followed by column chromatography of resulting residue afforded **16** in 94% (0.31 g) as colorless oil. $[\alpha]_D^{25}$ +16.0 (*c* 1.5, $CHCl_3$); IR (neat): 2933, 2859, 1589, 1492, 1376, 1253, 1174, 1099, 1004, 958, 835, 808, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (ddt, *J*=17.1, 10.5, 6.6 Hz, 1H), 5.05–4.92 (m, 2H), 3.99 (dq, *J*=8.4, 6.3 Hz, 1H), 3.80–3.69 (m, 1H), 3.53 (dd, *J*=8.4, 4.2 Hz, 1H), 2.06 (m, 2H), 1.59–1.38 (m, 4H), 1.39 (s, 3H), 1.37 (s, 3H), 1.29 (d, *J*=6.3 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 114.5, 107.7, 84.6, 72.7, 71.9, 33.7, 32.4, 27.3, 26.9, 25.9, 25.1, 18.8, 18.2, −4.1, −4.6.

2.1.10. Preparation of (+)-hydroxy-*exo*-brevicomin (5). A mixture of $PdCl_2$ (9 mg, 0.05 mmol) and CuCl (0.35 g, 3.6 mmol) in 10 mL of DMF and 2.5 mL of water were stirred under O_2 atmosphere at room temperature for 1.5 h. A solution of olefin **16** (0.09 g, 0.27 mmol) in minimum amount of DMF was added to the above mixture at room temperature. The reaction mixture was stirred for 5 h, under oxygen atmosphere at the same temperature. After the reaction was complete (TLC), it was poured into 3 N HCl (5 mL), and extracted with ether (3×5 mL). The combined ethereal extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvent followed by column chromatography of the resulting residue yielded (+)-hydroxy-*exo*-brevicomin **5** as colorless oil (35 mg, 74%). $[\alpha]_D$ +61.2 (*c* 2.4, $CHCl_3$), lit.[6a] $[\alpha]_D$ +61.3 (*c* 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (br s, 1H), 3.77 (d, *J*=7.2 Hz, 1H), 3.63 (dq, *J*=7.2, 6.3 Hz, 1H), 2.58 (br s, 1H), 1.95–1.75 (m, 2H), 1.72–1.61 (m, 3H), 1.52–1.46 (m, 1H), 1.45 (s, 3H), 1.14 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.4, 83.8, 76.5, 69.2, 34.6, 27.6, 24.8, 18.4, 17.1.

2.1.11. Preparation of (4*R*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-4-(iodomethyl)-2,2-dimethyl-1,3-dioxolane (18). To a solution of **15** (0.15 g, 0.34 mmol) in 4 mL of acetone was added sodium iodide (0.15 g, 1 mmol) at room temperature, under argon atmosphere and the reaction mixture was refluxed for 14 h. After reaction was complete (TLC), it was cooled, poured into water (6 mL), and extracted with ether (3×6 mL). Combined ethereal extracts were washed with satd sodium thiosulphate, brine, and dried (Na_2SO_4). Evaporation of solvent followed by column chromatography of the resulting residue afforded **18** as colorless oil in 94% (0.128 g) yield. $[\alpha]_D$ −15 (*c* 1, $CHCl_3$); IR (neat): 2927, 2856, 1602, 1463, 1375, 1253, 1074, 835, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (qd, *J*=6.3, 4.5 Hz, 1H), 3.90–3.82 (m, 1H), 3.71 (dd, *J*=7.5, 4.2 Hz, 1H), 3.41 (dd, *J*=10.8, 4.2 Hz, 1H), 3.28 (dd, *J*=10.8, 5.7 Hz, 1H), 1.45 (s, 3H), 1.40 (s, 3H), 1.19 (d, *J*=6.3 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.3, 83.7, 75.3, 67.5, 27.6, 27.3, 25.8, 18.7, 18.0, 7.9, −4.6, −4.7; HRMS for $C_{14}H_{29}IO_3Si$+Na calcd 423.0828; found 423.0807.

2.1.12. Preparation of (4*S*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxyethyl)-4-(4-oxopentyl)-2,2-dimethyl-1,3-dioxolane (19). To a refluxing solution of **18** (0.12 g, 0.3 mmol) and methylvinyl ketone (0.25 mL, 3 mmol) in 6 mL benzene was added a benzene (3 mL) solution of Bu_3SnH (0.16 mL, 0.6 mmol) and AIBN (10 mg, 0.06 mmol) dropwise over a period of 10 min. The reaction mixture was refluxed for further 1.5 h. It was cooled, poured into 1% aq NH_3 (6 mL) and extracted with ether (3×10 mL). Combined ethereal extracts were washed with 1% aq NH_3, water, brine, and dried (Na_2SO_4). Residue obtained after evaporation of solvent was purified by column chromatography to yield **19** in 63% (0.065 g, 71% based on starting material recovery) as colorless oil. $[\alpha]_D$ −17.3 (*c* 1.5, $CHCl_3$); IR (neat): 2985, 2857, 1718, 1473, 1369, 1253, 1159, 1105, 1070, 950, 877, 809, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94–3.84 (m, 2H), 3.53 (dd, *J*=8.1, 4.2 Hz, 1H), 2.47 (t, *J*=6.9 Hz, 2H), 2.13 (s, 3H), 1.80–1.43 (m, 4H), 1.37 (s, 3H), 1.36 (s, 3H), 1.57 (d, *J*=6.6 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 108.2, 84.0, 76.4, 67.7, 43.5, 33.1, 29.8, 27.4, 26.9, 25.8, 20.6, 19.1, 18.1, −4.6, −4.8; HRMS for $C_{18}H_{36}O_4Si$+Na calcd 367.2281; found 367.2280.

2.1.13. Preparation of (−)-hydroxy-*exo*-brevicomin (5). To a solution of **19** (40 mg, 0.11 mmol) in 2 mL of CH_2Cl_2 was added $FeCl_3\cdot 6H_2O$ (0.11 g, 0.4 mmol) at room temperature, under argon atmosphere. The reaction mixture was stirred for 3 h, filtered through a short pad of Celite and Celite pad was washed with ether (10 mL). The ethereal layer was washed with satd Na_2CO_3, brine, and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by column chromatography to yield (−)-**5** in 76% (0.015 g) as colorless oil. $[\alpha]_D$ −62.5 (*c* 0.8, $CHCl_3$), lit. $[\alpha]_D$ +61.3 (*c* 1.18, $CHCl_3$) for the (+)-enantiomer (vide supra); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (br s, 1H), 3.77 (d, *J*=7.2 Hz, 1H), 3.63 (dq, *J*=7.2, 6.3 Hz, 1H), 2.57 (br s, 1H), 1.90–1.76 (m, 2H), 1.70–1.57 (m, 3H), 1.52–1.44 (m, 1H), 1.45 (s, 3H), 1.14 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.5, 83.8, 76.5, 69.2, 34.6, 27.6, 24.8, 18.4, 17.1.

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