Enantioselective Total Synthesis of Some Brevicomins Using Aldolase Antibody 38C2

Benjamin List, Doron Shabat, Carlos F. Barbas III,* and Richard A. Lerner*

Abstract: Aldolase antibody 38C2 (Aldrich no. 47,995-0) catalyzes the aldol reaction between hydroxyacetone and aldehyde **7** to give dihydroxyketone **8*α*** in an enantiomeric excess (*ee*) >99%. This reaction has been performed on a semi-preparative scale to give the product in 55% yield (*ee* = 98%). Aldol **8*α*** can be converted to hydroxybrevicomins *ent*-**5** and *ent*-**6** by reduction and acid-catalyzed cyclization. Antibody 38C2 also catalyzes the retro-aldol reaction of racemic *syn*-**8**. After 52% conversion, the enantiomeric product (**8*β***) is obtained in >99% *ee*. By using either antibody-catalyzed aldol or retro-aldol reactions, both aldol enantiomers can be prepared with a single antibody catalyst. This methodology has been applied in highly enantioselective total syntheses of ten brevicomins.

Keywords: aldol reactions · antibody catalysis · brevicomin · enantioselective catalysis · total synthesis

Introduction

One major goal in chemistry is the development of efficient catalysts for enantioselective processes. Although a number of powerful catalysts for functional group transformations like redox reactions have been developed in the last two decades, far fewer examples of enantioselective *C–C bond-forming* catalysts of general use are known.[1] In this regard, the catalytic enantioselective aldol reaction, which is arguably one of the most important C–C bond-forming reactions, constitutes a great challenge.[2]

Using the process of reactive immunization, we recently developed aldolase antibody 38C2, which uses the enamine mechanism of natural occurring class I aldolases.[3] We have shown that, in contrast to its natural enzyme counterparts, and indeed most catalytic antibodies, this antibody aldolase accepts a wide variety of substrates.[4,5] Antibody 38C2 has been shown to be useful in organic synthesis as demonstrated by the highly enantioselective synthesis of the Wieland–Miescher ketone on a preparative scale.[6] While an antibody has been used previously in a total synthesis of (−)-α-multistriatin,[7] most catalytic antibodies reported to date have lacked the synthetic scope required of a generally useful catalyst. Here we report highly enantioselective total syntheses of (−)-(1*R*)-1-hydroxy-*exo*-brevicomin (*ent*-**6**) and (−)-(1*S*)-1-hydroxy-*exo*-brevicomin (*ent*-**5**) as well as formal total syntheses of eight different other brevicomins utilizing this antibody catalyst. The key steps are achieved by using either an antibody catalyzed aldol addition or retro-aldol reaction.

Derivatives of the 6,8-dioxabicyclo[3.2.1]octanes (Figure 1) are pheromones of a variety of bark beetle species.[8] Extensive outbreaks of bark beetles may result in the destruction of millions of trees per year causing great ecological and economic damage.[9] (+)-*Exo*-brevicomin (7-

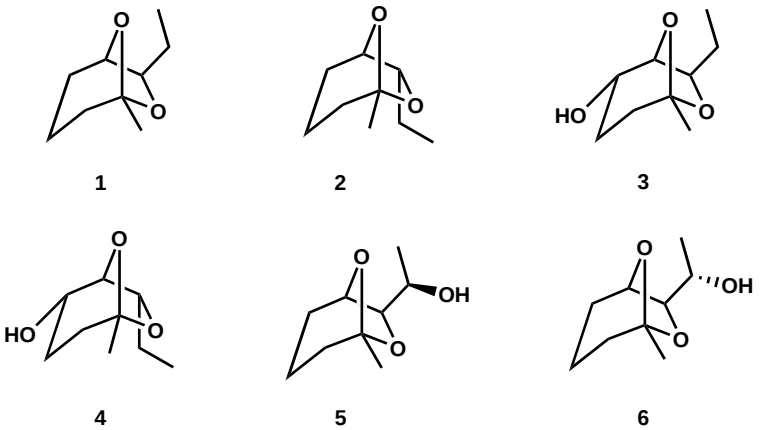

Figure 1. Structure of some brevicomins: (+)-*exo*-brevicomin (**1**); (+)-*endo*-brevicomin (**2**); (1*R*,2*S*,5*S*,7*R*)-2-hydroxy-*exo*-brevicomin (**3**); (1*R*,2*S*,5*S*,7*S*)-2-hydroxy-*endo*-brevicomin (**4**); (1*R*,1′*R*,5′*R*,7′*R*)-1-hydroxy-*exo*-brevicomin (**5**); (1*S*,1′*R*,5′*R*,7′*R*)-1-hydroxy-*exo*-brevicomin (**6**).

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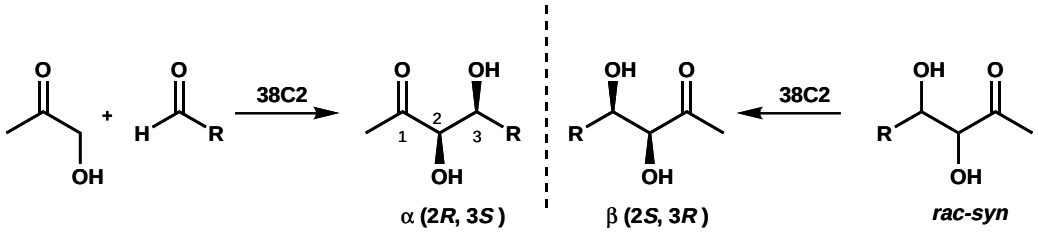


Scheme 1. The sterochemical course of 38C2-catalyzed aldol and retroaldol reactions involving hydroxyacetone.

ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (**1**) was the first member of this pheromone family to be identified.[8] Several oxygenated *exo*-brevicomins have been isolated and synthesized recently.[10,11] (+)-1-Hydroxy-*exo*-brevicomin and (+)-2-hydroxy-*exo*-brevicomin have been identified in the volatiles of the male mountain pine beetle, *Dentroctonus brevicomis*. Since its discovery in 1989 and structural elucidation in 1996, 1-hydroxy-exo-brevicomin has been synthesized twice. The first synthesis by Francke et al. was based on a kinetic resolution by Sharpless asymmetric epoxidation.[10b] The second by Mori et al. used the Sharpless asymmetric dihydroxylation (AD) as the key step.[10c] Using this methodology, they have also reported the synthesis of the (+)-2-hydroxy-*exo*-brevicomins.[10d]

We have previously demonstrated that 38C2-catalyzed aldol reactions with hydroxyacetone as donor lead to the highly regio- and stereoselective formation of α,β-dihydroxyketones with an $\alpha(2R,3S)$ configuration.[4] Further, unlike any of the transition metal catalyst reported to date,[2] these antibodies also efficiently catalyze the retro-aldol reaction. Kinetic resolution with these catalysts results in the selective destruction of the $\alpha(2R,3S)$-aldol allowing the recovery of the $\beta(2S,3R)$-aldol in high enantiomeric excess. By using both the aldol addition and retro-aldol activities, both aldol enantiomers may be prepared using the same antibody catalyst (Scheme 1).[12]

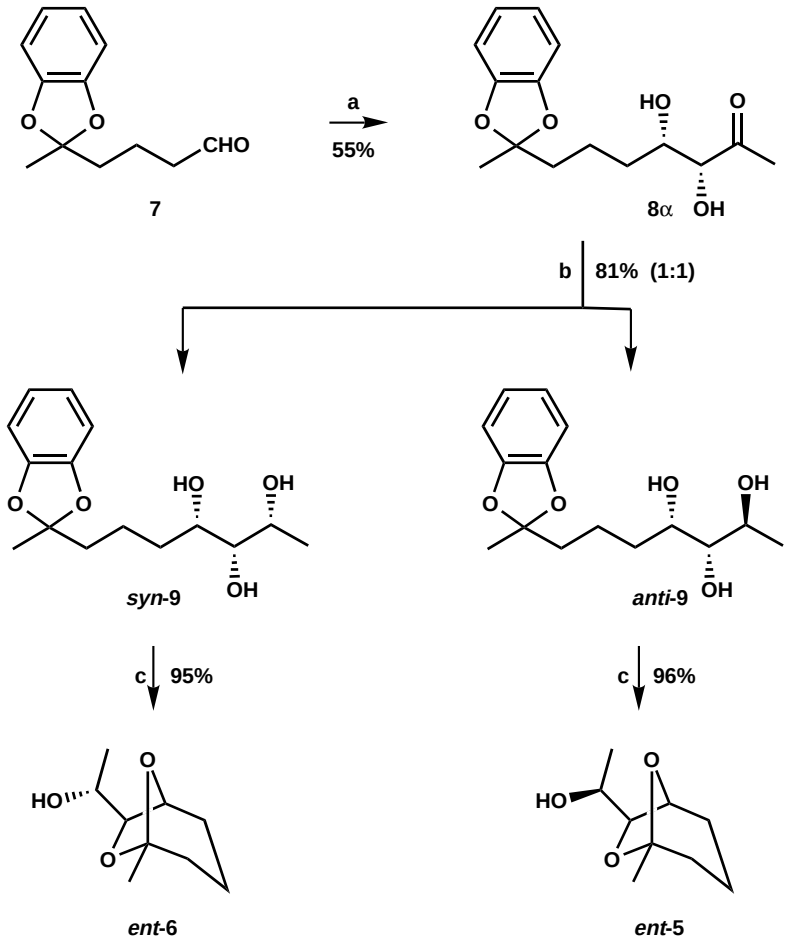
Results and Discussion

Antibody 38C2 catalyzes the aldol reaction between aldehyde **7** and hydroxyacetone on a preparative scale to give diol **8*α*** in 55% yield and 98% *ee* along with the *anti*-diastereomer (ratio 4:1).[13] On an analytical scale, the *ee* was even higher (>99%). Dihydroxyketone **8*α*** was reduced with sodium borohydride to give triols *syn*-**9** and *anti*-**9** after separation by HPLC. Acid-catalyzed deprotection and cyclization of the individual triols afforded hydroxybrevicomins *ent*-**5** and *ent*-**6** in essentially enantiomeric pure form (Scheme 2).

The *ee* of dihydroxyketone **8*α*** was determined by chiral HPLC analysis using a chiracell AD column. Its absolute configuration was assigned by comparison with synthetic reference samples prepared from aldehyde **7** by a Horner–Wadsworth–Emmons reaction followed by a Sharpless asymmetric dihydroxylation using either AD mix-α or AD mix-β. [14,15] (Figure 2)

Antibody 38C2 catalyzed retro-aldol reaction of racemic **8** gave diol **8*β*** in >99% *ee* after 52% conversion of the racemate, through a kinetic resolution. Thus, hydroxybrevicomins **5** and **6** can be obtained from **8*β*** by a route analogous to that described in Scheme 2.

2-Hydroxylated brevicomins **3** and **4** were prepared from dihydroxyketone **11*α*** by using a strategy similar to that described for copounds **5** and **6** (Scheme 3). Antibody 38C2 catalyzed the aldol reaction between aldehyde **10** and 1-hydroxy-2-butanone to give **11*α*** in >99% *ee*.[16] Again the enantiomers (*ent*-**3** and *ent*-**4**) could be prepared by kinetic resolution of aldol *rac-syn*-**11** to give **11*β*** in >99% *ee* after



Scheme 2. a) Antibody 38C2 (0.66 mol%), hydroxyacetone (5 vol%), phosphate buffered saline (PBS, pH 7.4); b) $NaBH_4$, MeOH; HPLC separation; c) *p*TsOH, C_6H_6, 60 °C.

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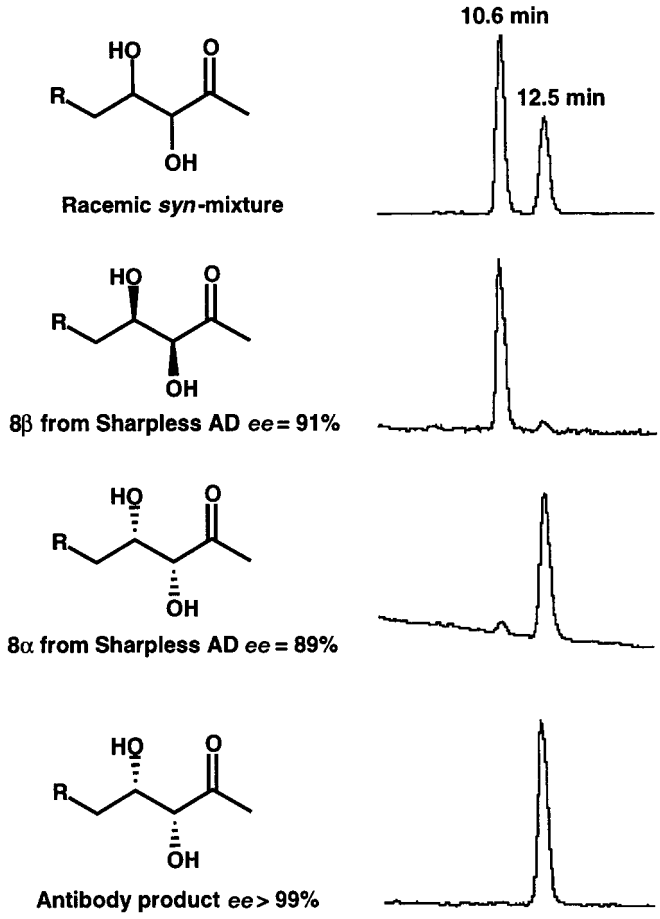


Figure 2. Determination of the absolute configuration and enantiomeric purity of aldol **8*α*** from an analytical scale reaction. Chiracell AD column (12% *i*PrOH/hexane, 1 mL min^{-1}, $\lambda = 284$ nm).

54% conversion. 2-Hydroxy-*exo*-brevicomin **4** is a new compound that has not been reported previously, and we suggest that it may be a natural product derived from *endo*-brevicomin **2** by oxygenation. This is supported by the fact that *exo*-brevicomin **1** is the precursor in the biosynthesis of hydroxy-brevicomin **3**.[10a] The synthesis of *exo*-brevicomin **1** from **3** has already been reported.[17] Thus, both enantiomers of *exo*-brevicomin **1** are accessible now.

The kinetic parameters of all antibody catalyzed reactions are shown in Table 1.

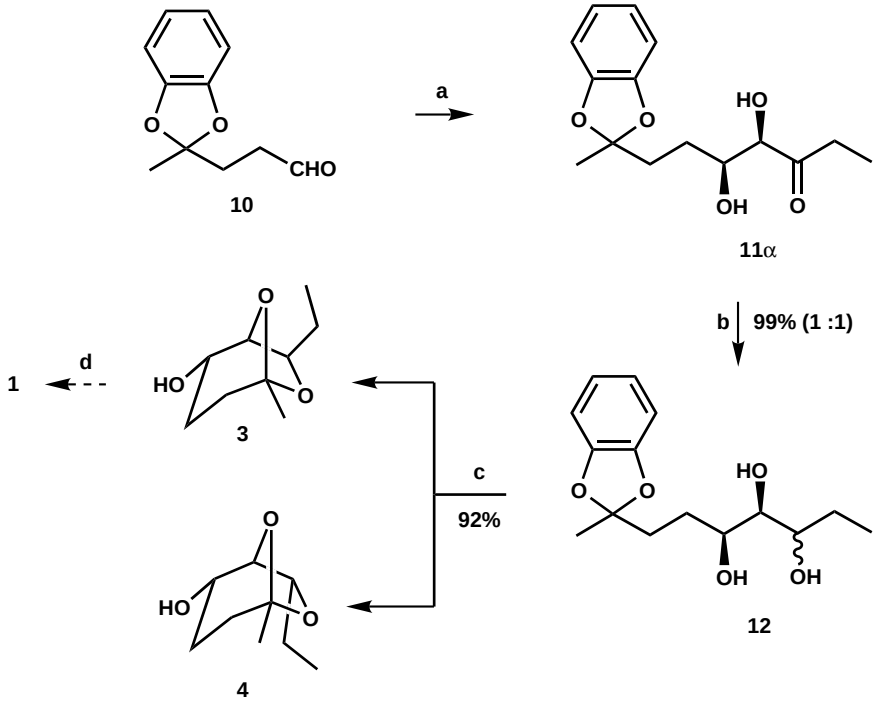
Table 1. Kinetic parameters of antibody-catalyzed reactions.

Compound	rate[a]	*ee* [%]	dr (*syn*:*anti*)
8*α*	0.65 min^{-1}[b]	> 99	4:1
8*β*	0.03 min^{-1}[b]	> 99	-
11*α*	0.24[c]	> 99	5:1
11*β*	0.24[c]	> 99	-

[a] No product formation was observed in the background reactions after three days. [b] k_{cat} obtained from Lineweaver–Burk plots. [c] Rates were measured at a single concentration and are relative to the rates found for compounds **8*α*** and **8*β***.

Conclusion

In summary we have demonstrated highly enantioselective total syntheses of brevicomins *ent*-**5** and *ent*-**6**, and formal total syntheses of eight other brevicomins (**5**, **6**, **3**, *ent*-**3**, **4**, *ent*-**4**, **1**, *ent*-**1**) by utilizing *a single antibody catalyst*. For the first time, a catalytic antibody has been used to decrease the total number of synthetic steps and to increase the enantioselectivity of natural product syntheses. These results underscore the power of reactive immunization to generate antibody catalysts that are both efficient and broad in scope.



Scheme 3. a) Analytical scale reaction: antibody 38C2 (0.6 mol%), 1-hydroxy-2-butanone (5 vol%), PBS (pH 7.4); b) $NaBH_4$, MeOH; c) *p*TsOH, C_6H_6, 60 °C, column chromatography; d) ref. [17].

Experimental Section

Aldehyde 7: 5-Oxohexanenitrile (1.14 mL, 10 mmol, 1 equiv), catechol (5.51 g, 50 mmol, 5 equiv), and a catalytic amount of *p*-TsOH were refluxed in benzene (15 mL) for 12 h. After cooling to room temperature, the mixture was diluted with ether (50 mL) and washed four times with 1N NaOH and once with saturated ammonium chloride. The mixture was dried ($MgSO_4$), filtered, and concentrated to give 2 g (> 99%) of the acetal as slightly yellow oil. This was taken up in dichloromethane (100 mL) and treated at −78 °C with 1N DIBAH (10.5 mL) in hexanes. After 2 h at −78 °C and 1 h at 0 °C, saturated ammonium chloride (3 mL) and diethyl ether (100 mL) were added and the mixture was allowed to warm to room temperature. A small amount of alumina and after 10 min magnesium sulfate were added. The mixture was stirred for two hours and then filtered and concentrated. Flash chromatography (9% EtOAc/hexane) gave 1545 mg (75%) of aldehyde **7** as an oil. Spectroscopic data of the acetal: ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.63$ (s, 3H), 1.88 (m, 2H), 2.07 (m, 2H), 2.40 (t, $J = 7.1$, 2H),

6.77 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 17.0, 19.2, 24.5, 37.7, 108.4, 117.8, 119.2, 121.2; HRMS: calcd for $C_{12}H_{13}NO_2$: 203.0946, obs 203.0952. Spectroscopic data for aldehyde **7**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.60$ (s, 3H), 1.80 (m, 2H), 1.93 (m, 2H), 2.48 (dt, $J = 1.4$ and 7.2, 2H), 6.74 (m, 4H), 9.74 (t, $J = 1.4$, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 15.7$, 24.3, 38.1, 43.3, 108.2, 121.0, 121.2, 201.8; HRMS: calcd for $C_{12}H_{14}O_3$: 206.0943, obs 206.0948.

Antibody-catalyzed synthesis of diol 8*α*: To a solution of antibody 38C2 (36 μM, 18 mL) in PBS buffer (50 mM, pH = 7.0) was added hydroxyacetone (1 mL) and aldehyde **7** in acetonitrile (20.6 mg, 0.1 mmol, 1 mL of a 100 mM solution). The final concentrations were about 33 μM (0.66% relative to the aldehyde) of 38C2, 0.68 M of hydroxyacetone, and 5 mM of aldehyde **7**. After 36 h the reaction reached 65% conversion as monitored by RP-HPLC (35% acetonitrile/water with 0.1% TFA, retention time of **8*α*** = 7.75 min, *anti* isomer = 7.34 min, **7** = 15.77 min). The antibody was separated from the reaction by centrifugation in Centricon-10 concentrator tubes (Amicon). The solvent was removed under reduced pressure and the crude product was purified by RP-HPLC, to give pure **8*α*** (10.2 mg, 0.036 mmol, 55% according to consumed aldehyde) in more than 98% *ee* (the *ee* was determined by chiral HPLC analysis using a chiracell AD column (12% *i*PrOH/hexane, 1 mL min^{-1}, $\lambda = 284$ nm; on an analytical scale the *ee* was >99%). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.46-2.10$ (m's, 7H), 1.59 (s, 3H), 2.23 (s, 3H), 3.73 (br, 1H), 3.95 (br, 1H), 4.03 (br, 1H), 6.73 (m, 4H).^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 19.4$, 24.2, 25.1, 34.0, 38.7, 71.5, 79.1, 108.2, 118.5, 120.9, 207.9. HRMS calcd for $C_{15}H_{20}O_5Na$: 303.1208, obs 303.1216.

Triols 9: Diol **8*α*** (10.2 mg, 0.036 mmol, 1 equiv) in MeOH (10 mL) was treated with sodium boranate (3 mg, 2 equiv) and stirred for 5 min.The mixture was extracted with saturated ammonium chloride solution and re-extracted with diethyl ether. After drying ($MgSO_4$) and evaporation in vacuum, the diastereomeric triols were isolated by RP-HPLC. *anti*-**9** (3.9 mg, 0.014 mmol, 38%) and *syn*-**9** (4.4 mg, 0.016 mmol, 43%) were obtained as solids. Spectroscopic data of *anti*-**9**: ^{1}H NMR (250 MHz, CD_3OD): $\delta = 1.08$ (d, $J = 6.3$, 3H), 1.45 (s, 3H), 1.30–1.60 (m, 4H), 1.89 (m, 2H), 2.98 (br, 1H), 3.61 (m, 2H), 6.59 (m, 4H).^{13}C NMR (63 MHz, CD_3OD): $\delta = 19.8$, 20.6, 24.5, 34.6, 40.1, 69.7, 73.0, 78.3, 109.1, 122.0, 148.9; HRMS calcd for $C_{15}H_{22}O_5Na$: 305.1365, obs 305.1375. Spectroscopic data of *syn*-**9**: ^{1}H NMR (250 MHz, CD_3OD): $\delta = 1.05$ (d, $J = 6.4$, 3H), 1.43 (s, 3H), 1.30–1.60 (m, 4H), 1.80 (m, 2H), 2.99 (br, 1H), 3.48 (br, 1H), 3.67 (m, 1H), 6.60 (m, 4H).^{13}C NMR (63 MHz, CD_3OD): $\delta = 20.1$, 20.8, 24.5, 34.6, 40.1, 68.7, 71.2, 78.3, 109.1, 120.0, 122.0, 148.9; HRMS calcd for $C_{15}H_{22}O_5Na$: 305.1365, obs 305.1374.

(1*S*,1′*S*,5′*S*,7′*S*)-1-(5′-Methyl-6′,8′-dioxabicyclo[3.2.1]oct-7′yl)ethanol ((−)-(1*S*)-1-Hydroxy-*exo*-brevicomin (*ent*-5)): Triol *anti*-**9** (4.4 mg, 0.016 mmol) and a catalytic amount of *p*-TsOH in benzene (0.5 mL) was heated to 60 °C for 45 min. After cooling, one drop of 25% aqueous trimethylamine and silica gel (100 mg) were added. This material was evaporated in vacuum, and then chromatographed (9% EtOAc/hexane) to give 1-hydroxybrevicomin *ent*-**5** (2.7 mg, 0.0154 mmol, 96%). The spectroscopic data are in full agreement with literature values. The *ee* was determined by chiral GC according to reference [10d] to be 98%.

(1*R*,1′*S*,5′*S*,7′*S*)-1-(5′-Methyl-6′,8′-dioxabicyclo[3.2.1]oct-7′yl)ethanol ((−)-(1R)-1-Hydroxy-*exo*-brevicomin (*ent*-6)): Triol *syn*-**9** (3.9 mg, 0.014 mmol) and a catalytic amount of *p*-TsOH in benzene (0.5 mL) was heated to 60 °C for 45 min. After cooling, one drop of 25% aqueous trimethylamine and silica gel (100 mg) were added. This material was evaporated in vacuum, and then chromatographed (9% EtOAc/hexane) to give 1-hydroxybrevicomin *ent*-**6** (2.3 mg, 0.013 mmol, 95%) as a liquid. The spectroscopic data are in full agreement with literature values. The *ee* was determined by chiral GC according to reference [10d] to be 98%.

Antibody catalyzed kinetic resolution of diol 8: This reaction was performed on an analytical scale. Racemic aldol **8** (500 μM) and antibody 38C2 (30 μM) in PBS (pH 7.4) were incubated until 52% of the racemic mixture was consumed (ca. 10 h). The remaining aldol **8*β*** was isolated with an analytical RP-HPLC column and the *ee* was determined as described above to be >99%.

Chemical reference syntheses of 8*α* and 8*β* by Horner–Wadsworth–Emmons reaction and Sharpless asymmetric dihydroxylation: **Horner–Wadsworth–Emmons reaction**: Aldehyde **7** (360 mg, 1.748 mmol, 1 equiv), diethyl(2-oxopropyl) phosphonate (424 mg, 2.184 mmol, 1.25 equiv) and lithum hydroxide monohydrate (101 mg, 2.412 mmol, 1.38 equiv) were stirred in anhydrous THF (5 mL) for 3 h. The mixture was diluted with diethyl ether (5 mL), and saturated ammonium chloride solution (0.3 mL) was added. The mixture was dried ($MgSO_4$), filtered, and concentrated. Filtration over silica gel (50% EtOAc/hexane) gave 430 mg (>99%) of the *α*,*β*-nsaturated methyl ketone as a liquid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.60$ (s, 3H), 1.58–1.70 (m, 2H), 1.90–2.00 (m, 2H), 2.22 (s, 3H), 2.20–2.30 (m, 2H), 6.05 (d, $J = 15.9$, 1H), 6.75 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 19.2, 24.5, 26.8, 32.0, 37.6, 108.2, 108.3, 120.9, 121.2, 131.5, 147.3, 203.8. HRMS calcd for $C_{15}H_{18}O_3Na$: 269.1154, obs 269.1161.

Diol 8*α* by Sharpless asymmetric dihydroxylation: The *α*,*β*-unsaturated methyl ketone (300 mg, 1.22 mmol, 1 equiv) in *t*BuOH/water (12 mL; 1:1) was treated with AD-mix-*α* (1.73 g) and methanesulfonamide (120 mg) at 0 °C and stirred for 3 h at 0 °C and then for 16 h at room temperature. Sodium metabisulfite (2.48 g) was carefully added and the mixture was extracted with ethyl acetate (5×). After drying ($MgSO_4$), evaporation in vacuum, and chromatography (35% EtOAc/hexane) the pure diol **8*α*** (299 mg, 88%) was obtained as a solid. The *ee* was determined as described above to be 89%.

Diol 8*β* by Sharpless asymmetric dihydroxylation: The *α*,*β*-unsaturated methyl ketone (300 mg, 1.22 mmol, 1 equiv) in *t*BuOH/water (12 mL; 1:1) was treated with AD-mix-*β* (1.73 g) and methanesulfonamide (120 mg) at 0 °C and stirred for 3 h at 0 °C and then for 16 h at room temperature. Sodium metabisulfite (2.48 g) was carefully added and the mixture was extracted with ethyl acetate (5×). After drying ($MgSO_4$), evaporation in vacuum, and chromatography (35% EtOAc/hexane) the pure diol **8*β*** (290 mg, 85%) was obtained as a solid. The *ee* was determined as described above to be 91%.

Chemical reference syntheses of diol 11*α* and diol 11*β* by the Mulzer sequence and Sharpless asymmetric dihydroxylation:[18,15] Aldehyde 10: Ethyl levulinate (7.1 mL, 50 mmol, 1 equiv), catechol (27.53 g, 250 mmol, 5 equiv), and a catalytic amount *p*-TsOH were refluxed in benzene (200 mL) for 12 h. After cooling to room temperature, the mixture was diluted with ether (250 mL) and washed four times with 1N NaOH and once with saturated ammonium chloride. The mixture was dried ($MgSO_4$), filtered, and concentrated to give the levulinate acetal (11.8 g, >99%) as a slightly yellow oil. This material (2.36 g, 10 mmol) was taken up in dichloromethane (100 mL) and treated at −78 °C with 1N DIBAH (10.5 mL) in hexanes. After 30 min at −78 °C, saturated ammonium chloride (3 mL) and diethyl ether (100 mL) were added and the mixture was allowed to warm to room temperature. A small amount of alumina and subsequently after 10 min magnesium sulfate were added. The mixture was stirred for two hours and then filtered and concentrated. For the following chemical step, this material was pure enough. For the antibody-catalyzed step: Flash chromatography (9% EtOAc/hexane) gave aldehyde **10** (1.83 g, 95%) as an oil. Spectroscopic data of the acetal: ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.12$ (t, $J = 7.1$, 3H); 1.53 (s, 3H), 2.20 (m, 2H), 2.38 (m, 2H), 4.02 (q, $J = 7.1$, 2H), 6.66 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 14.1$, 24.6, 28.2, 34.2, 60.53, 108.4, 121.14, 147.3, 172.8; spectroscopic data of **10**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.64$ (s, 3H), 2.31 (t, $J = 7.6$, 2H), 2.62 (t, 7.6, 2H), 6.76 (m, 4H), 9.76 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 24.6$, 31.4, 37.6, 108.4, 121.3, 147.1, 200.8.

***α*,*β*-Unsaturated ethyl ketone:** Methyl methanephosphonate (1.95 mL, 18 mmol, 3.6 equiv) in anhydrous diethyl ether (15 mL) was treated at −78 °C with a 2.5 M solution of *n*BuLi (7.2 mL, 18 mmol, 3.6 equiv). After 30 min the ester (881 mg, 10 mmol, 2 equiv) in anhydrous diethyl ether (7 mL) was slowly added and the mixture was stirred for 1 h at −78 °C and then for 30 min at 0 °C. Water (360 mg, 20 mmol, 4 equiv) in THF (40 mL) and then aldehyde **10** (960 mg, 5 mmol, 1 equiv) were added. After 1 h, the mixture was diluted with diethyl ether (65 mL) and saturated ammonium chloride solution (3 mL) was added. The mixture was dried ($MgSO_4$), filtered, and concentrated. Chromatography (9% EtOAc/hexane) gave the *α*,*β*-unsaturated ethyl ketone (960 mg, 78%) as a liquid. ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.06$ (t, $J = 7.3$, 3H), 1.62 (s, 3H), 2.09 (m, 2H), 2.37 (m, 2H), 2.50 (q, $J = 7.3$, 3H), 6.04 (dt, $J = 1.5$ and 15.8, 1H), 6.75 (m, 4H), 6.81 (dt, $J = 6.8$ and 15.8, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 8.0$, 24.6, 26.1, 33.3, 37.5, 108.3, 117.9, 121.1, 130.7, 145.2, 147.2, 200.7. HRMS calcd for $C_{15}H_{18}O_3$: 246.1256, obs 246.1262.

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Diol 11*α*: The α,β-unsaturated ethyl ketone (400 mg, 1.626 mmol, 1 equiv) in *t*BuOH/water (16 mL; 1:1) was treated with AD-mix-α (2.3 g) and methanesulfonamide (160 mg) at 0 °C, and stirred for 3 h at 0 °C and then for 36 h at room temperature. Sodium metabisulfite (3.38 g) was carefully added and the mixture was extracted with ethyl acetate (5 ×). After drying ($MgSO_4$), evaporation in vacuum, and chromatography (gradient, 35%, 50% EtOAc/hexane) the pure diol **11*α*** (355 mg, 78%; *ee* = 91%, HPLC) was obtined as a solid together with the starting material (85 mg, 21%). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.12$ (t, $J = 7.3$, 3H), 1.64 (s, 3H), 1.86 (m, 3H), 2.15 (m, 2H), 2.52 (m, 2H), 3.75 (br, 1H), 4.00 (br, 1H), 4.05 (br, 1H), 6.77 (m, 4H).^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 7.4$, 28.2, 31.0, 35.4, 71.6, 78.6, 108.4, 118.6, 121.1, 147.7, 210.6. HRMS calcd for $C_{15}H_{20}O_5Na$: 303.1208, obs 303.1198.

Diol 11*β*: The α,β-unsaturated ethyl ketone (400 mg, 1.626 mmol, 1 equiv) in *t*BuOH/water (16 mL, 1:1) was treated with AD-mix-β (2.3 g) and methyl sulfonamide (160 mg) at 0 °C and stirred for 3 h at 0 °C and then for 36 h at room temperature. Sodium metabisulfite (3.38 g) was carefully added and the mixture was extracted with ethyl acetate (5 ×). After drying ($MgSO_4$), evaporation in vacuum, and chromatography (gradient, 35%, 50% EtOAc/hexane) the pure diol **11*β*** (322 mg, 71%; *ee* = 92%, HPLC) was obtained as a solid and together with the starting material (114 mg, 28%). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.12$ (t, $J = 7.3$, 3H), 1.64 (s, 3H), 1.86 (m, 3H), 2.15 (m, 2H), 2.52 (m, 2H), 3.75 (br, 1H), 4.00 (br, 1H), 4.05 (br, 1H), 6.77 (m, 4H).^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 7.4$, 28.2, 31.0, 35.4, 71.6, 78.6, 108.4, 118.6, 121.1, 147.7, 210.6.

Synthesis of diol 11*α* by antibody catalysis: This reaction was performed on an analytical scale. Aldehyde **10** (500 μM), 1-hydroxy-2-butanone (5% v/v), and antibody 38C2 (30 μM) were incubated for about 5 h. The aldol product was separated on an analytical RP-HPLC column and the *ee* (>99%) was determined as mentioned in the preparation of diol **8*α***.

Kinetic resolution of diol 11 by antibody catalysis: This reaction was performed on an analytical scale. Racemic aldol **11** (5 mM) and antibody 38C2 (104 μM) in PBS (pH 7.4) were incubated until 54% of the racemic mixture was consumed (ca. 10 h). The remaining aldol **11*β*** was isolated with an analytical RP-HPLC column and the *ee* was determined as described above to be >99%.

Synthesis of 2-hydroxybrevicomins 3 and 4: Triols 12: Diol **11*α*** from Sharpless AD, *ee* = 91% (140 mg, 0.5 mmol, 1 equiv) in MeOH (5 mL) was treated with sodium boranate (38 mg, 2 equiv) and stirred for 5 min. The mixture was extracted with saturated ammonium chloride solution and re-extracted with diethyl ether. After drying ($MgSO_4$) and evaporation in vacuum, pure diastereomeric triols **12** (141 mg, >99%) were isolated. For analytical reasons the triols can be separated by RP-HPLC. Spectroscopic data for *anti*-**12**: ^{1}H NMR (250 MHz, CD_3OD): $\delta = 0.86$ (t, $J = 7.1$, 3H), 1.25 (m, 1H), 1.49 (s, 3H), 1.60 (m, 3H), 1.85 (m, 1H), 2.00 (m, 1H), 3.00 (br, 1H), 3.40 (br, 1H), 3.72 (br, 1H), 6.60 (m, 4H).^{13}C NMR (63 MHz, CD_3OD): $\delta = 10.2$, 24.6, 27.4, 28.5, 36.8, 71.5, 74.1, 76.7, 109.1, 120.0, 122.1, 149.0; HRMS calcd for $C_{15}H_{22}O_5Na$: 305.1365, obs 305.1358. *syn*-**12**: HRMS calcd for $C_{15}H_{22}O_5Na$: 305.1365, obs 305.1371.

(1*R*,2*S*,5*S*,7*R*)- and (1*R*,2*S*,5*S*,7*S*)-7-Ethyl-5-methyl-6,6-dioxabicyclo[3.2.1]octan-2-ol) ((+)-(2*S*)-2-Hydroxy-*exo*-brevicomin and (+)-(2*S*)-2-Hydroxy-*endo*-brevicomin (4 and 3). Triols **12** (141 mg, 0.5 mmol) and a catalytic amount of *p*-TsOH in benzene (10 mL) were heated to 60 °C for 45 min. After cooling the mixture, 25% aqueous trimethylamine (30 drops) and silica gel (500 mg) were added. This material was evaporated in vacuum, and then chromatographed (gradient 9%, 12% EtOAc/hexane) to give **4** (40 mg, 46%) as a solid and **3** (40 mg, 46%) as a liquid. The spectroscopic data of **3** are in full agreement with literature values:[10c] ^{1}H NMR (250 MHz, C_6D_6): $\delta = 0.90$ (t, $J = 7.4$, 3H), 1.12 (br, 1H), 1.43 (s, 3H), 1.30–1.70 (m, 6H), 3.62 (m, 1H), 3.80 (d, $J = 3.7$, 1H), 4.18 (t, $J = 6.5$, 1H).^{13}C NMR (63 MHz, C_6D_6): $\delta = 10.0$, 24.3, 26.9, 28.8, 35.4, 66.2, 77.3, 80.9, 107.4. Spectroscopic data of **4**: ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 0.96$ (t, $J = 7.4$, 3H), 1.02 (br, 1H), 1.48 (s, 3H), 1.67–2.10 (m, 6H), 3.32 (dt, $J =$ 3.1 and 8.1, 1H), 3.52 (dd, $J = 4.1$ and 9.0, 1H), 4.30 (m, 1H).^{13}C NMR (63 MHz, $CDCl_3$) δ 9.5, 23.5, 23.6, 25.4, 33.8, 68.1, 74.9, 78.0.

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