Supporting Information

Design and Synthesis of Benzene Congeners of Resolvin E2, a Proresolving Lipid Mediator, as Its Stable Equivalents

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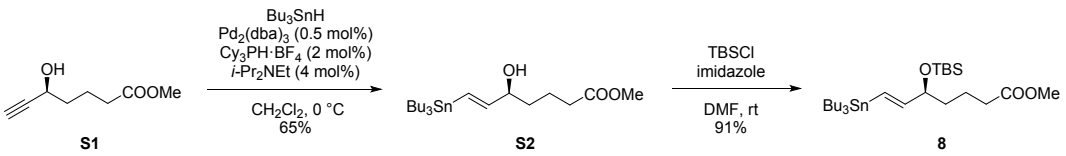
General Procedures

NMR spectra were measured on JEOL ECX400P (400 MHz), JEOL EXP400 (400 MHz) and JEOL ECA500 (500 MHz). Chemical shifts were reported in the δ scale relative to tetramethylsilane (TMS) as 0.00 ppm for ^{1}H ($CDCl_3$) and residual $CHCl_3$ (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C), CH_3OH (3.31 ppm for ^{1}H and 49.0 ppm for ^{13}C) as internal reference. Mass spectra (MS) were measured on JEOL JMS-HX110, JEOL JMS-T100GCV, JEOL JMS-T100LCP, JEOL JMS-700TZ (ESI). Optical rotation was measured on JASCO DIP-1030. Silica gel column chromatography and flash column chromatography was carried out with Wakogel 60N (Wako Pure Chemical Industries, Ltd., neutral, 63-212 μm) and silica gel 60N (Kanto Chemical Co., Inc., spherical, neutral, 40-50 μm), respectively. All reactions were carried out under an argon atmosphere using flame-dried or oven-dried glassware, unless otherwise noted, and monitored with analytical TLC (Merck Ltd., TLC Silica gel 60 F_{254}).

Experimental Procedures



Methyl (*S,E*)-5-hydroxy-7-(tributylstannyl)hept-6-enoate (S2)

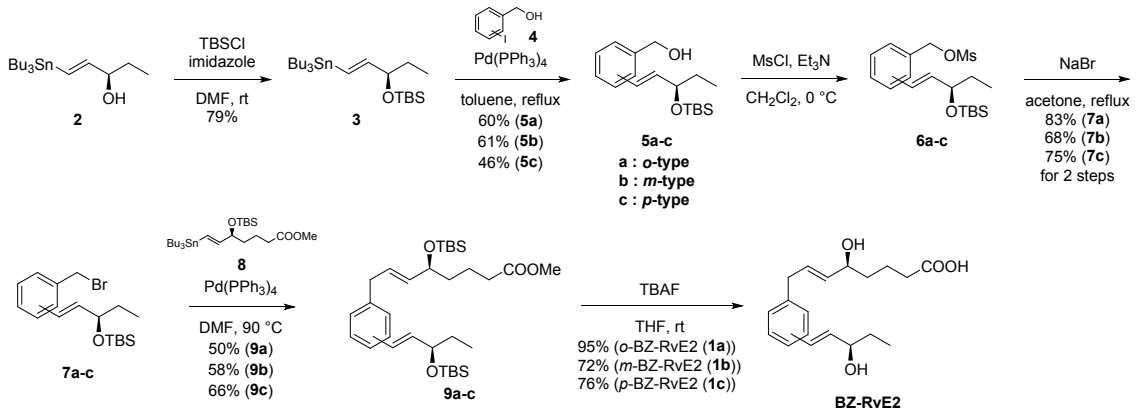
To a stirred solution of $Cy_3PH{\cdot}BF_4$ (88.0 mg, 0.24 mmol) and *i*-Pr_2NEt (84 μL, 0.48 mmol) in CH_2Cl_2 (60 mL) was added $Pd_2(dba)_3$ (55 mg, 60 μmol) at room temperature. The resulting solution was stirred at the same temperature for 10 min. After **S1**[1] (1.87 g, 12.0 mmol, >99% ee) and Bu_3SnH (3.9 mL, 14.4 mmol) in CH_2Cl_2 was added to the reaction mixture at 0 °C, the mixture was stirred at the same temperature overnight and concentrated. The residue was purified by silica gel column chromatography (K_2CO_3 - SiO_2 = 1 : 9, AcOEt - hexane = 1 : 8) to give **S2** (3.5 g, 7.83 mmol, 65%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (dd, *J* = 19.2, 1.0 Hz, 1H), 5.99 (dd, *J* = 19.2, 5.2 Hz, 1H), 4.08 (m, 1H), 3.67 (s, 3H), 2.36 (t, *J* = 7.6 Hz, 1H), 1.81-0.80 (m, 27H). Data for **S2** agreed with previous data[2].

Methyl (*S,E*)-5-((*tert*-butyldimethylsilyl)oxy)-7-(tributylstannyl)hept-6-enoate (8)

To a stirred solution of **S2** (3.5 g, 7.83 mmol) in DMF (52 mL) was added imidazole (2.13 g, 31.3 mmol) and TBSCl (2.36 g, 15.7 mmol) at room temperature. The mixture was stirred at the same temperature for 12 h and quenched by addition of H_2O and extracted with AcOEt/hexane (1 : 4). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash silica gel column chromatography (K_2CO_3 - SiO_2 = 1 : 9, AcOEt - hexane = 1 : 8) to give **8** (4.0 g, 7.12 mmol, 91%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (d, *J* = 19.2 Hz, 1H), 5.89 (dd, *J* = 19.2, 6.0 Hz, 1H), 4.04 (dt, *J* = 6.0, 6.0 Hz, 1H), 3.66 (s, 3H), 2.32 (t, *J* = 7.4 Hz, 1H), 1.72-1.25 (m, 16H), 0.96-0.78 (m, 25H), 0.04 (s, 3H), 0.02 (s, 3H). Data for **8** agreed with previous data[3].



(*R*,*E*)-1-(Tributylstannyl)pent-1-en-3-ol (3)

To a stirred solution of **2**[4] (2.0 g, 5.4 mmol, 95% ee) in DMF (52 mL) was added imidazole (1.47 g, 21.6 mmol) and TBSCl (1.62 g, 10.8 mmol) at room temperature. The mixture was stirred at the same temperature for 12 h and quenched by addition of H_2O and extracted with AcOEt/hexane (1 : 4). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash silica gel column chromatography (K_2CO_3 - SiO_2 = 1 : 9, AcOEt - hexane = 1 : 10) to give **3** (2.1 g, 4.28 mmol, 79%) as a colorless oil.

$[\alpha]^{15}_D$ +19.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (dd, *J* = 19.3, 0.8 Hz, 1H), 5.91 (dd, *J* = 19.3, 5.5 Hz, 1H), 3.96 (dt, *J* = 5.5, 5.5 Hz, 1H), 1.54-1.40 (m, 8H), 1.30 (tq, *J* = 7.5, 7.5 Hz, 6H), 0.94-0.81 (m, 27H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 126.6, 78.2, 31.0, 29.3, 27.4, 26.1, 18.5, 13.9, 10.0, 9.6; LRMS (ESI) *m/z* 513.25 [$(M+Na)^+$]; HRMS (EI) calcd for $C_{19}H_{41}OSSn$: 433.1949 [$(M–Bu)^+$], found: 433.1951.

(*R*,*E*)-(2-(3-((*Tert*-butyldimethylsilyl)oxy)pent-1-en-1-yl)phenyl)methanol (5a)

To a stirred solution of **3** (510 mg, 1.04 mmol) and *o*-iodobenzyl alcohol (**4a**) (268 mg, 1.14 mmol) in toluene (10 mL) was added $Pd(PPh_3)_4$ (60 mg, 50 μmol) at room temperature. The mixture was refluxed overnight, quenched by addition of sat. NH_4Cl aq. and extracted with AcOEt. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash silica gel column chromatography (K_2CO_3 - SiO_2 = 1 : 9, AcOEt - hexane = 1 : 4) to give **5a** (191 mg, 0.623 mmol, 60%) as a yellow oil.

$[\alpha]^{24}_D$ +31.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (m, 1H), 7.37 (m, 1H), 7.30-7.23 (m, 2H), 6.81 (d, *J* = 15.6 Hz, 1H), 6.11 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.75 (d, *J* = 3.6 Hz, 2H), 4.23 (dt, *J* = 6.4, 5.2 Hz, 1H), 1.65-1.55 (m, 3H), 0.93 (s, 9H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 136.3, 136.2, 128.3, 128.2, 127.6, 126.4, 125.7, 74.8, 63.6, 31.3, 26.0, 18.4, 9.8, –4.2, –4.6; LRMS (ESI) *m/z* 329.15 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{18}H_{30}NaO_2Si$: 329.1913 [$(M+Na)^+$], found: 329.1922.

(*R*,*E*)-(3-(3-((*Tert*-butyldimethylsilyl)oxy)pent-1-en-1-yl)phenyl)methanol (5b)

Similar to the synthesis of **5a**, **5b** was prepared from 3-iodobenzyl alcohol (**4b**) in 61% yield.

$[\alpha]^{23}_{D}$ +37.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 3H), 7.22 (s, 1H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.20 (dd, *J* = 16.0, 6.4 Hz, 1H), 4.69 (s, 2H), 4.20 (dt, *J* = 6.0, 6.0 Hz, 1H), 1.70-1.56 (m, 3H), 1.08-0.76 (m, 12H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 137.7, 133.9, 128.9, 128.9, 126.0, 125.8, 125.0, 74.8, 65.5, 31.4, 26.1, 18.5, 9.8, –4.1, –4.6; LRMS (ESI) *m/z* 329.15 [$(M+Na)^+$]; HRMS (ESI) calcd for calcd for $C_{18}H_{30}NaO_2Si$: 329.1913 [$(M+Na)^+$], found: 329.1910.

(*R*,*E*)-(4-(3-((*Tert*-butyldimethylsilyl)oxy)pent-1-en-1-yl)phenyl)methanol (5c)

Similar to the synthesis of **5a**, **5c** was prepared from 4-iodobenzyl alcohol (**4c**) in 46% yield.

$[\alpha]^{25}_{D}$ +44.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.17 (dd, *J* = 16.0, 6.4 Hz, 1H), 4.68 (d, *J* = 4.0 Hz, 2H), 4.20 (dt, *J* = 6.0, 6.0 Hz, 1H), 1.64-1.56 (m, 2H), 0.92 (s, 9H), 0.92 (t, *J* = 7.6 Hz, 3H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 136.9, 133.6, 128.7, 127.4, 126.7, 74.9, 65.3, 31.4, 26.1, 18.5, 9.8, –4.1, –4.6; LRMS (ESI) *m/z* 329.10 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{18}H_{30}NaO_2Si$: 329.1913 [$(M+Na)^+$], found: 329.1915.

(*R*,*E*)-((1-(2-(Bromomethyl)phenyl)pent-1-en-3-yl)oxy)(*tert*-butyl)dimethylsilane (7a)

To a stirred solution of **5a** (6.0 mg, 20 μmol) and Et_3N (3.0 μL, 22 μmol) in CH_2Cl_2 (0.2 mL) was added MsCl (2.0 μL, 22 μmol) at 0 °C. The mixture was stirred at the same temperature for 1 h, quenched by addition of brine and extracted with AcOEt. The combined organic extracts were dried (Na_2SO_4) and concentrated to give crude **6a**.

To a stirred solution of crude **6a** in acetone (0.2 mL) was added NaBr (6.0 mg, 58 μmol) at room temperature. The mixture was refluxed for 12 h, quenched by addition of brine and extracted with AcOEt. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (AcOEt - hexane = 1 : 20) to give **7a** (6.0 mg, 16 μmol, 83% for 2 steps) as a colorless oil.

$[\alpha]^{21}_{D}$ +20.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz 1H), 7.30 (m, 2H), 7.21 (m, 1H), 6.86 (d *J* = 15.6 Hz, 1H), 6.16 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.55 (d, *J* = 2.8 Hz, 2H), 4.27 (dt, *J* = 6.0, 6.0 Hz, 1H), 1.62 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.95 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.8, 134.7, 130.4, 129.2, 127.7, 126.9, 125.3, 74.6, 31.9, 31.3, 26.1, 18.4, 9.7, –4.1, –4.6; LRMS (ESI) *m/z* 369.35 [$(M+H)^+$]; HRMS (EI) calcd for calcd for $C_{16}H_{24}BrOSi$: 339.0780 [$(M–Et)^+$], found: 339.0779.

(*R*,*E*)-((1-(3-(Bromomethyl)phenyl)pent-1-en-3-yl)oxy)(*tert*-butyl)dimethylsilane (7b)

Similar to the synthesis of **7a**, **7b** was prepared from **5b** in 68% yield.

$[\alpha]^{23}_{D}$ +32.9 (*c* 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.31-7.20 (m, 3H), 6.48 (d, *J* = 16.4 Hz, 1H), 6.20 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.49 (s, 2H), 4.20 (dt, *J* = 6.0, 6.0 Hz, 1H), 1.59 (m, 2H), 0.95-0.89 (m, 12H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 138.4, 134.6, 129.5, 128.8, 128.3, 127.4, 126.9, 75.0, 34.0, 31.7, 26.4, 18.8, 10.1, –3.8, –4.3; LRMS (ESI) *m/z* 369.15 [$(M+H)^+$]; HRMS (EI) calcd for calcd for $C_{18}H_{29}BrOSi$: 368.1171 (M^+), found: 368.1173.

(*R,E*)-((1-(4-(Bromomethyl)phenyl)pent-1-en-3-yl)oxy)(*tert*-butyl)dimethylsilane (7c)

Similar to the synthesis of **7a**, **7c** was prepared from **5c** in 75% yield.

$[\alpha]^{23}_{D}$ +43.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.43 (s, 4H), 6.48 (dd, *J* = 16.0, 1.6 Hz, 1H), 6.19 (dd, *J* = 16.0, 6.4 Hz, 1H), 4.50 (s, 2H), 4.20 (m, 1H), 1.63-1.55 (m, 2H), 0.92 (m, 12H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 136.8, 134.4, 129.4, 128.4, 126.9, 74.8, 33.7, 31.3, 26.1, 18.5, 9.8, –4.2, –4.6; LRMS (ESI) *m/z* 391.20 [$(M+Na)^+$]; HRMS (EI) calcd for calcd for $C_{18}H_{29}BrOSi$: 368.1171 (M^+), found: 368.1167.

Methyl (*S,E*)-5-((*tert*-butyldimethylsilyl)oxy)-8-(2-((*R,E*)-3-((*tert*-butyldimethylsilyl)oxy) pent-1-en-1-yl)phenyl)oct-6-enoate (9a)

To a stirred solution of **7a** (60 mg, 0.162 mmol) and **8** (148 mg, 0.243 mmol) in DMF (1.8 mL) was added $Pd(PPh_3)_4$ (9.0 mg, 8.0 μmol) at room temperature. The mixture was at 90 °C overnight, quenched by addition of brine and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (K_2CO_3 - SiO_2 = 1 : 9, AcOEt - hexane = 1 : 8) and EPCLC (conditions; Yamazen Ultra Pack Si-40A, hexane:AcOEt = 97:3, flow rate; 10 mL/min, detection; UV 254 nm) to give **9a** (45 mg, 80 μmol, 50%) as a colorless oil.

$[\alpha]^{19}_{D}$ +7.21 (*c* 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 1H), 7.19-7.15 (m, 2H), 7.11 (m, 1H), 6.71 (d, *J* = 16.0 Hz, 1H), 6.03 (dd, *J* = 16.0, 6.4 Hz, 1H), 5.70 (dt, *J* = 15.2, 6.4 Hz, 1H), 5.38 (dd, *J* = 15.6, 6.8 Hz, 1H), 4.20 (dt, *J* = 6.0, 6.0 Hz, 1H), 4.07 (dt, *J* = 6.0, 6.0 Hz, 1H), 3.66 (s, 3H), 3.38 (d, *J* = 6.4 Hz, 2H), 2.29 (t, *J* = 7.6 Hz, 2H), 1.70-1.55 (m, 4H), 1.51-1.41 (m, 2H), 0.92 (t, *J* = 7.6 Hz, 3H), 0.92 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H), 0.01 (s, 3H), –0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 137.5, 136.3, 135.4, 134.9, 129.6, 128.6, 127.5, 126.7, 126.6, 126.3, 75.0, 73.2, 51.6, 37.8, 35.8, 34.1, 31.4, 26.1, 26.0, 21.0, 18.4, 18.3, 9.9, –4.1, –4.1, –4.6, –4.7; LRMS (ESI) *m/z* 583.35 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{32}H_{56}NaO_4Si_2$: 583.3615 [$(M+Na)^+$], found: 583.3636.

Methyl (*S,E*)-5-((*tert*-butyldimethylsilyl)oxy)-8-(3-((*R,E*)-3-((*tert*-butyldimethylsilyl)oxy) pent-1-en-1-yl)phenyl)oct-6-enoate (9b)

Similar to the synthesis of **9a**, **9b** was prepared from **7b** in 58% yield.

$[\alpha]^{19}_{D}$ +16.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.16 (m, 3H), 7.03 (d, *J* = 6.8 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.15 (dd, *J* = 16.0, 6.4 Hz, 1H), 5.69 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.48 (dd, *J* = 15.2, 6.4 Hz, 1H), 4.19 (dt, *J* = 6.0, 6.0 Hz, 1H), 4.10 (dt, *J* = 6.4, 6.4 Hz, 1H), 3.66 (s, 3H), 3.34 (d, *J* = 6.4 Hz, 2H), 2.31 (t, *J* = 7.6 Hz, 2H), 1.68-1.47 (m, 6H), 0.92-0.87 (m, 21H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 140.7, 137.5, 135.1, 133.4, 129.2, 129.1, 128.7, 127.7, 126.7, 124.3, 75.0, 73.2, 51.6, 38.7, 37.9, 34.2, 31.4, 26.1, 26.0, 21.0, 18.5, 18.4, 9.8, 0.14, –4.0, –4.1, –4.6, –4.6; LRMS (ESI) *m/z* 583.35 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{32}H_{56}NaO_4Si_2$: 583.3615 [$(M+Na)^+$], found: 583.3631.

Methyl (*S,E*)-5-((*tert*-butyldimethylsilyl)oxy)-8-(4-((*R,E*)-3-((*tert*-butyldimethylsilyl)oxy) pent-1-en-1-yl)phenyl)oct-6-enoate (9c)

Similar to the synthesis of **9a**, **9c** was prepared from **7c** in 66% yield.

$[\alpha]^{18}_{D}$ +29.0 (*c* 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.13 (dd, *J* = 16.0, 6.3 Hz, 1H), 5.67 (dt, *J* = 15.0, 6.5 Hz, 1H), 5.46 (dd, *J* = 15.0, 6.5 Hz, 1H), 4.18 (dt, *J* = 6.0, 6.0 Hz, 1H), 4.09 (dt, *J* = 6.0, 6.0 Hz, 1H), 3.66 (s, 3H), 3.33 (d, *J* = 6.5 Hz, 2H), 2.31 (t, *J* = 7.3 Hz, 2H), 1.70-1.44 (m, 6H), 0.95-0.79 (m, 21H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 139.6, 135.2, 135.0, 132.8, 129.0, 128.9, 128.9, 126.5, 75.0, 73.2, 51.6, 38.4, 37.8, 34.2, 31.4, 26.1, 26.0, 21.0, 18.5, 18.4, 9.9, –4.0, –4.1, –4.6, –4.6; LRMS (ESI) *m/z* 583.35 [$(M+Na)^+$]; HRMS (ESI) calcd for $C_{32}H_{56}NaO_4Si_2$: 583.3615 [$(M+Na)^+$], found: 583.3629.

***o*-BZ-RvE2 (1a)**

To a stirred solution of **9a** (5.0 mg, 8.9 μmol) in THF (18 μL) was added TBAF (1.0 M in THF, 54 μL, 54 μmol) at room temperature. The mixture was stirred at the same temperature for 24 h. After the reaction was completed, the mixture was added phosphate buffer (pH 6) and extracted with AcOEt. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash silica gel column chromatography (MeOH - $CHCl_3$ = 1 : 30) to give *o*-BZ-RvE2 (**1a**) (2.7 mg, 8.5 μmol, 95%) as a colorless oil.

$[\alpha]^{19}_{D}$ +1.45 (*c* 0.25, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (m, 1H), 7.16 (m, 3H), 6.83 (d, *J* = 16.0 Hz, 1H), 6.08 (dd, *J* = 16.0, 6.4 Hz, 1H), 5.79 (dt, *J* = 15.6, 6.0 Hz, 1H), 5.37 (dd, *J* = 15.6, 6.8 Hz, 1H), 4.14 (dt, *J* = 6.8, 6.8 Hz, 1H), 4.00 (dt, *J* = 6.4, 6.4 Hz, 1H), 3.44 (d, *J* = 6.0 Hz, 2H), 2.24 (t, *J* = 7.2 Hz, 2H), 1.68-1.44 (m, 6H), 0.98 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 180.2, 138.7, 137.4, 135.5, 135.3, 130.9, 130.7, 128.8, 128.6, 127.6, 127.0, 75.1, 73.2, 38.0, 36.9, 31.3, 23.0, 10.3; LRMS (ESI) *m/z* 316.95 [$(M–H)^–$]; HRMS (ESI) calcd for $C_{19}H_{25}O_4$: 317.1753 [$(M–H)^–$], found:317.1749; HPLC purity >99% (COSMOSIL 5C18-MS- Ⅱ 4.6mm x 250mm,

CH_3CN/H_2O/TFA = 35/65/0.01, 1.0 mL/min, t_R= 11.7 min, detection 254 nm)

***m*-BZ-RvE2 (1b)**

Similar to the synthesis of **1a**, *m*-BZ-RvE2 (**1b**) was prepared from **9b** in 72% yield.
$[\alpha]^{19}_D$ –1.31 (*c* 0.18, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (m, 3H), 7.07 (m, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.20 (dd, *J* = 16.0, 6.8 Hz, 1H), 5.79 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.52 (dd, *J* = 15.6, 6.8 Hz, 1H), 4.11 (dt, *J* = 6.8, 6.8 Hz, 1H), 4.11 (dt, *J* = 6.8, 6.8 Hz, 1H), 3.36 (d, *J* = 6.8 Hz, 2H), 2.30 (t, *J* = 7.2 Hz, 2H), 1.66-1.50 (m, 6H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 177.9, 142.1, 138.8, 135.7, 133.7, 131.5, 131.5, 129.9, 129.1, 127.9, 125.4, 75.3, 73.3, 39.7, 38.0, 35.1, 31.5, 22.5, 10.5; LRMS (ESI) *m/z* 316.90 [(M–Na)$^-$]; HRMS (ESI) calcd for $C_{19}H_{25}O_4$: 317.1753 [(M–H)$^-$], found: 317.1746; HPLC purity >99% (COSMOSIL 5C18-MS- Ⅱ 4.6mm x 250mm, CH_3CN/H_2O/TFA = 35/65/0.01, 1.0 mL/min, t_R= 11.5 min, detection 254 nm)

***p*-BZ-RvE2 (1c)**

Similar to the synthesis of **1a**, *p*-BZ-RvE2 (**1c**) was prepared from **9c** in 76% yield.
$[\alpha]^{18}_D$ +1.77 (*c* 0.43, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 7.31 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.16 (dd, *J* = 16.0, 6.5 Hz, 1H), 5.77 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.49 (dd, *J* = 15.5, 7.0 Hz, 1H), 4.09 (dt, *J* = 6.5, 6.5 Hz, 1H), 4.02 (dt, *J* = 7.0, 7.0 Hz, 1H), 3.34 (d, *J* = 6.5 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 1.70-1.46 (m, 6H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 177.7, 141.0, 136.4, 135.5, 132.8, 131.2, 131.1, 129.8, 127.5, 75.1, 73.1, 39.3, 37.8, 34.9, 31.3, 22.3, 10.3; LRMS (ESI) *m/z* 316.90 [(M–Na)$^-$]; HRMS (ESI) calcd for $C_{19}H_{25}O_4$: 317.1753 [(M–H)$^-$], found: 317.1749; HPLC purity 98% (COSMOSIL 5C18-MS- Ⅱ 4.6mm x 250mm, CH_3CN/H_2O/TFA = 35/65/0.01, 1.0 mL/min, t_R= 11.0 min, detection 254 nm)

Murine peritonitis evaluation

Male BALB/c mice (6–7 weeks; Japan SLC, Shizuoka, Japan) were used. Heat-killed *Propionibacterium acnes* (*P. acnes*; 500 μg per mouse) was injected intraperitoneally. At 12 h after *P. acnes* injection, 300 pg of RvE2, *o*-BZ-RvE2, *m*-BZ-RvE2, *p*-BZ-RvE2 or vehicle alone was administered intraperitoneally. At 12 h after *P. acnes* injection, three different doses (300 fg, 300 pg or 300 ng per mouse) of RvE2, *o*-BZ-RvE2 or vehicle alone was administered intraperitoneally. At 24 h after *P. acnes* injection, peritoneal exudate cells (PECs) were collected and counted. Results were expressed as percentage inhibition of *P. acnes*-induced increase in the number of PECs compared with vehicle alone. All animal procedures were conducted in accordance with the Hokkaido University animal ethics committee.

Metabolic stability

60 μL was taken from an ethanol solution (1 mg / 1 mL) of synthesized compound, and the solvent was removed. 0.1 M PBS buffer (435 μL, pH 7.4), CH_3CN (10 μL), NADPH Regeneration System A solution (25 μL), and NADPH Regeneration System B solution (5 μL) were added to each compound, and agitated with a vortex mixer. After incubation at 37 °C., Corning® UltraPool™ HLM 150 (25 μL) was added after 5 minutes, and 80 μL of the solution was dispensed every hour (after 0, 1, 2, 3, 6 hours). The dispensed solution was quenched by adding CH_3CN (80 μL), and each sample was centrifuged (10000 rpm) at room temperature for 3 minutes. The supernatant was analyzed using HPLC (COSMOSIL 5C18-MS-Ⅱ 4.6mm x 250mm, CH_3CN/H_2O/TFA = 35/65/0.01, 1.0 mL/min, detection 254 nm).

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Stable conformations of *m*-BZ-RvE2

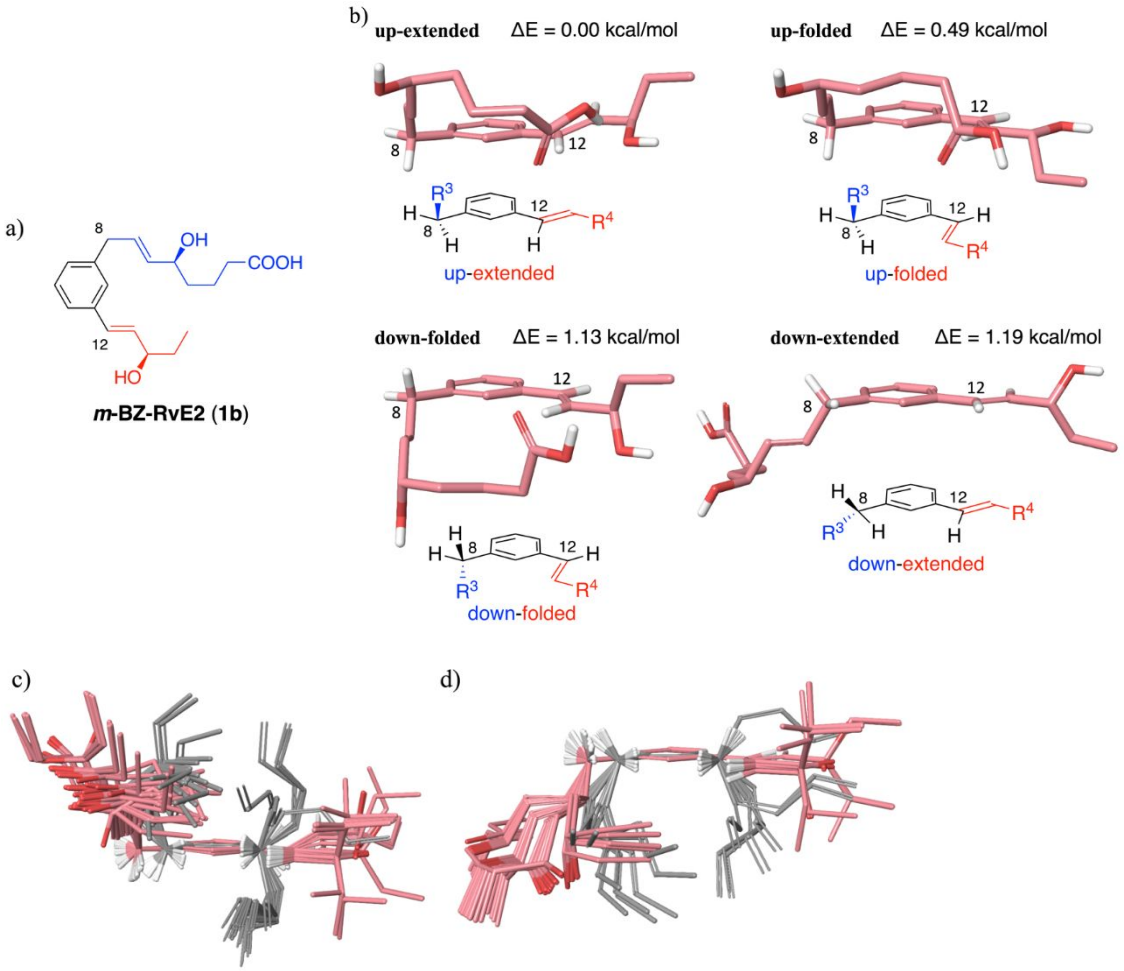

Figure S1. Stable conformations of *m*-BZ-RvE2 (**1b**) obtained by calculations. a) Chemical structure of *m*-BZ-RvE2. b) Four typical stable conformations. ΔE means the relative potential energy from the global minimum. c) Superimposition of the up-extended/folded forms of *m*-BZ-RvE2 (pink) on the up-up/down conformers of RvE2 (gray) within 2.0 kcal/mol from the global minimum conformation. d) Superimposition of the down-extended/folded forms of *m*-BZ-RvE2 (pink) on the down-up/down conformers of RvE2 (gray) within 2.0 kcal/mol from the global minimum conformation.