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Total Synthesis of Varitriol, Varioxirane, and Enantiomer of the Proposed Biosynthetic Precursor

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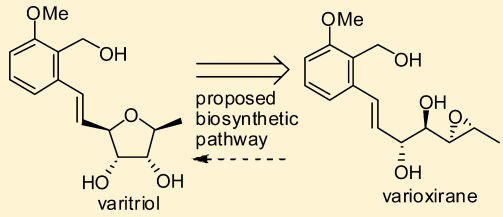
Supporting Information

ABSTRACT: The first stereoselective total synthesis of varioxirane was accomplished, and the proposed biosynthetic pathway was supported by converting varioxirane to (+)-varitriol. The first total synthesis of enantiomer of the proposed biosynthetic precursor, (1*E*,3*S*,4*R*,5*E*)-1-(2-(hydroxymethyl)-3-methoxyphenyl)hepta-1,5-diene-3,4-diol, was also achieved by utilizing the unreacted allylic alcohol obtained during the Sharpless kinetic resolution step. Other key steps include the Horner−Wadsworth−Emmons reaction and the diastereoselective reduction of α,β-unsaturated ketone to its corresponding alcohol.



Varitriol (**1**) and varioxirane (**2**) (Figure 1) were isolated from a marine-derived strain of the fungus *Emericella*

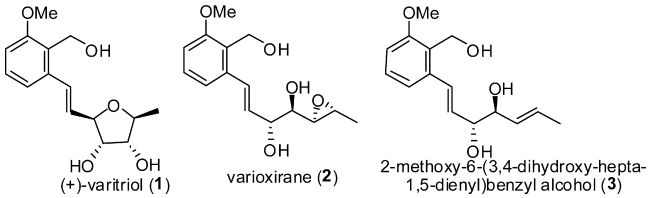


Figure 1. Natural products **1**−**3**.

variecolor in 2002.[1] Varitriol became a very attractive target for several synthetic organic chemistry groups after its isolation. To date, as many as 15 total syntheses[2] (among them, two are unnatural varitriol (*ent*-**1**),[3] one formal synthesis[4] and two analogues synthesis[5]) have been reported. This is because of the simple structure associated with high levels of biological activity toward renal, CNS, and breast cancer cell lines in the tested NCI's 60-cell panel.[1,6] Most of the syntheses relied on a chiral pool starting material such as D-ribose,[2a,b,f−h,3] γ-D-ribonolactone,[2d,i] D-mannitol,[2k] dimethyl L-tartrate,[2l] and methyl α-D-mannopyranoside.[2m] Although several synthetic approaches are available for **1**, neither the synthesis nor the absolute configuration was reported for varioxirane (**2**). However, Barrero and co-workers[1] proposed the relative configuration of **2** based on a hypothetical biogenetic relationship between **1** and **2**. The same group also proposed that the biosynthesis of **1** might be from 2-methoxy-6-(3,4-dihydroxyhepta-1,5- dienyl)benzyl alcohol (**3**),[7] which is a common metabolite of *Aspergillus variecolor* (the imperfect state of *E. variecolor*), via varioxirane (**2**).[1] The biosynthetic hypothesis is that enzymatic epoxidation of the corresponding double bond of **3** may yield **2** and intramolecular S_N2 epoxide opening of **2** would yield **1**.[1]

As part of our interest in developing synthetic strategies for bioactive natural products based on plausible biosynthetic pathways,[8] we envisaged that the total synthesis of varioxirane (**2**) would not only provide a new synthetic route to varitriol (**1**) but also provide support to the proposed biosynthetic pathway. Herein we report the short and efficient synthesis of varitriol (**1**) from varioxirane (**2**) and enantiomer of **3** (*ent*-**3**) by a developing new synthetic strategy that does not rely on chiral pool starting materials.

We anticipated that the functionality embedded frameworks like **4** (Figure 2) can easily provide varioxirane (**2**), whereas frameworks like **5** can provide **3** by simple transformations such as stereoselective reduction of α,β-unsaturated ketone and global deprotection of protecting groups. Enones **4** and **5** could be derived by reacting aromatic aldehyde **6** with β-ketophosphonates **7** and **8**, respectively, under Horner−Wadsworth−Emmons reaction conditions. These chiral β-ketophosphonates **7** and **8** could easily be obtained from a common starting material, α-hydroxy ester (±)-**9** in three steps such as the Sharpless asymmetric epoxidation/kinetic resolution, masking the free secondary hydroxyl group, and introducing phosphonate.

The synthesis began from the Sharpless kinetic resolution[9] of allylic alcohol (±)-**9**[10] using of (−)-DIPT, $Ti(^iOPr)_4$, and TBHP in CH_2Cl_2 to give the epoxy alcohol (+)-**10**[11] (er 98.89:1.11) in 42% yield (Scheme 1). Silylation of the secondary hydroxyl in **10** furnished **11**, which was treated with lithiated methyl phosphonate to afford β-ketophosphonate[12] **7** (R = TBS) in 89% yield (two steps). Coupling of ketophosphonate **7** under optimized reaction conditions (KHMDS, THF, −78 °C to rt) with the aromatic aldehyde **6** (R_1 = Ac), prepared following the literature procedure,[13]

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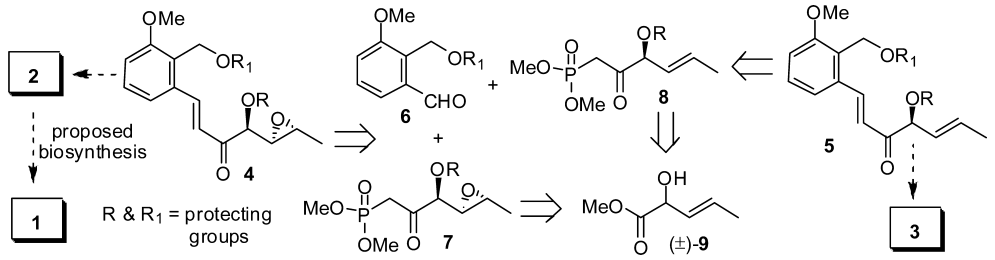
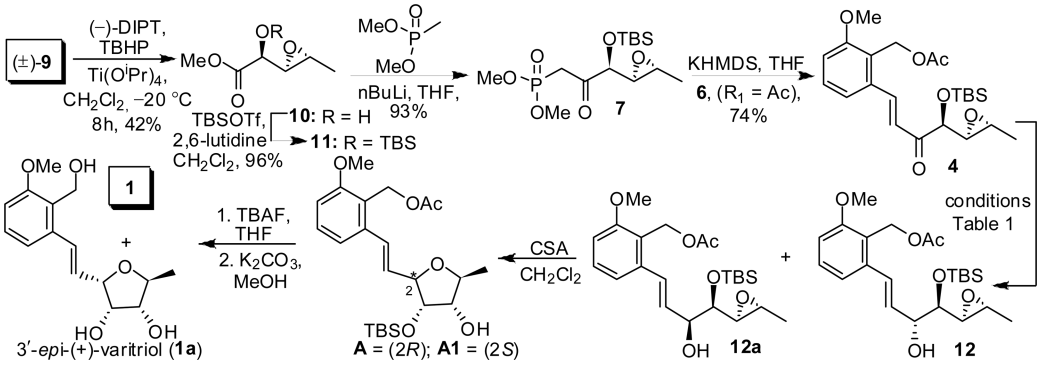


Figure 2. Synthetic plan for **1**−**3** and retrosynthetic plan for **4** and **5**.

Scheme 1. Synthesis of 12, 12a and 1, 1a



afforded the α,β-unsaturated ketone **4** (R = TBS, R_1 = Ac) in 74% yield.

We were now ready to investigate the key 1,2-reduction of ketone **4** to install the desired hydroxyl chiral center. Efforts to increase the *anti* selectivity under various reducing reagents yielded the undesired *syn* isomer as a major or exclusive product (Table 1). Reduction with $Zn(BH_4)_2$ at −20 °C[14] as well as at 0 °C resulted in undesired isomer **12a** as a major product (entries 1 and 2). Conversion of the chromatographically inseparable **12** and **12a** to separable **A** and **A1** (ratio of 1:2 and 92% combined yield) and subsequent deprotections of silyl and acetyl yielded **1** and 3′-*epi*-(+)-varitriol (**1a**), respectively. Identities of the major and minor products were determined by comparison of **1** with the literature.[1−3] A similar result was obtained with $LiEt_3BH$ at −78 °C[15] (1:2.3, entry 3), whereas at 0 °C there was no selectivity and only moderate yield (entry 4). K-Selectride and DIBAL-H[16] could not improve the desired selectivity (entries 5 and 6). Reduction with $NaBH_4/CeCl_3$ in MeOH[17] at 0 °C as well as at −50 °C gave exclusively undesired isomer **12a** (entries 7 and 8).

Table 1. Screening Reducing Agents for the *Anti*-Selective Reduction of 4 To Give 12

entry	conditions	yield[a] (%)	12:12a[b]
1	$Zn(BH_4)_2$, THF, −20 °C	87	1:2
2	$Zn(BH_4)_2$, THF, 0 °C	85	1:3.1
3	$LiEt_3BH$, THF, −78 °C	76	1:2.3
4	$LiEt_3BH$, THF, 0 °C	61	1:1
5	K-Selectride, THF, −78 °C	84	1:1.6
6	DIBAL-H, CH_2Cl_2, −78 °C	80	1:2
7	$NaBH_4/CeCl_3$, MeOH, 0 °C	82	only **12a**
8	$NaBH_4/CeCl_3$, MeOH, −50 °C	90	only **12a**

[a]Isolated yields. [b]The ratio was determined by ^{1}H NMR analysis

We then reasoned that the reduction of **4** with various reducing agents yielded *syn* isomer **12a** as a major product or exclusively because of the Felkin−Ahn control where a dihedral angle of ∼90° between the OTBS and carbonyl groups maximizes stereoelectronic interactions in the transition state (Figure 3A). It was expected that freeing a secondary hydroxyl group within **4** to **13** (scheme 2) might induce the stereoselectivity by the cyclic-Cram model (Figure 3B),[18] in which a proton of the hydroxyl group is hydrogen bonded to the carbonyl oxygen, enforcing a syn-periplanar relationship between the hydroxyl and carbonyl groups and leading to the desired *anti* isomer **14**.

Accordingly, a silyl group of **4** was removed by using HF−pyridine to give the epoxy alcohol **13** (Scheme 2), which was subjected to various reducing agents, and the results are

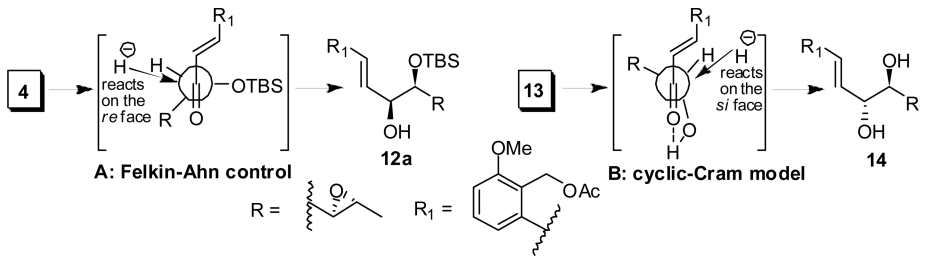


Figure 3. Felkin−Ahn and cyclic-Cram modes of stereocontrol.

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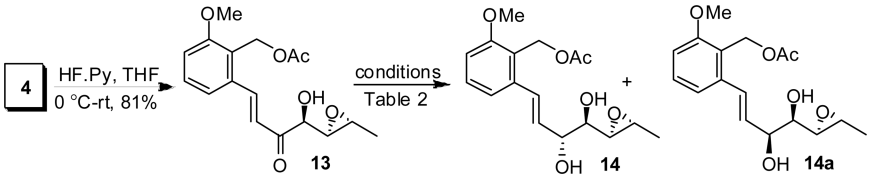
Scheme 2. Synthesis of 14 and 14a



illustrated in Table 2. In contrast to **4** (Table 1, entries 7 and 8), a reduction of **13** with $NaBH_4/CeCl_3$ in MeOH at 0 °C as well as at −50 °C found no selectivity (Table 2, entries 1 and 2). With $Zn(BH_4)_2$ in THF at 0 °C, the desired *anti* diol **14** was slightly improved (1.3:1, entry 3); however, at −78 °C with the same reagent the selectivity was completely lost (entry 4). With K-Selectride the level of selectivity was also poor (1.2:1, entry 5). Gratifyingly, the excellent selectivity of *anti* diol **14** (11.5:1, entry 6) was obtained with $LiEt_3BH$ in THF at −78 °C, and when the solvent was changed from THF to ether the selectivity and yield were further increased (32.3:1, entry 7).

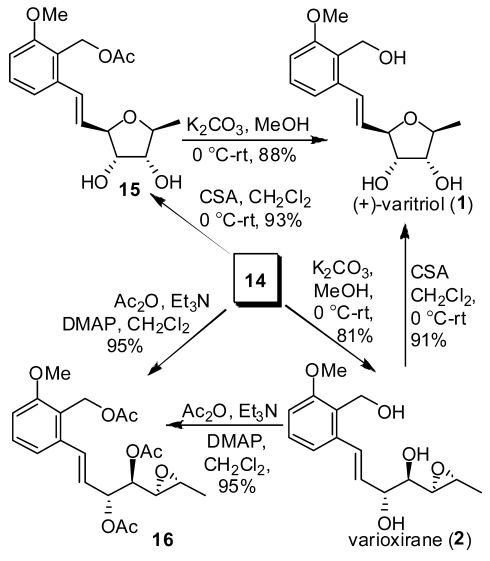
Table 2. Screening Reducing Agents for the *Anti*-Selective Reduction of 13 To Give 14

entry	conditions	yield[a] (%)	14:14a[b]
1	$NaBH_4/CeCl_3$, MeOH, 0 °C	77	1.1:1
2	$NaBH_4/CeCl_3$, MeOH, −50 °C	86	1.1:1
3	$Zn(BH_4)_2$, THF, 0 °C	76	1.3:1
4	$Zn(BH_4)_2$, THF, −78 °C	80	1:1
5	K-Selectride, −78 °C	70	1.2:1
6	$LiEt_3BH$, THF, −78 °C	73	11.5:1
7	$LiEt_3BH$, ether, −78 °C	82	32.3:1

[a]Isolated yield. [b]The ratio was determined by ^1H NMR analysis.

With the desired *anti* diol **14** in hand, to accomplish the target molecules two steps were needed to obtain varitriol (**1**) and one step to obtain varioxirane (**2**). Treatment of **14** with camphorsulfonic acid (CSA) in CH_2Cl_2 at 0 °C to rt effected intramolecular epoxide opening, as expected, to provide tetrahydrofuran moiety **15** in excellent yield (Scheme 3).

Scheme 3. Synthesis of Varitriol (1), Varioxirane (2), and Peracetylated Derivative of Varioxirane 16



Finally, deacetylation with K_2CO_3 in MeOH furnished varitriol (**1**) in 88% yield. The spectral data and specific rotation ($[\alpha]^{30}_D$ = +23.8 (*c* 0.26, CH_3OH); lit.[1] $[\alpha]^{25}_D$ = +18.5 (*c* 2.30, CH_3OH)) of **1** agree well with the literature data.[1−3]

We then turned our attention toward the total synthesis of varioxirane and converting it to varitriol to support the proposed biosynthetic pathway. The direct deacetylation of **14** provided varioxirane (**2**) in 81% yield. Treatment of **2** with Ac_2O (4 equiv) and Et_3N (6 equiv) furnished the peracetylated derivative of varioxirane **16**, which was also alternatively obtained from **14** using Ac_2O (2.5 equiv) and Et_3N (4 equiv). Spectral data and specific rotation ($[\alpha]^{30}_D$ = −32.9 (*c* 0.19, $CHCl_3$); lit.[1] $[\alpha]^{25}_D$ = −28.0 (*c* 0.31, $CHCl_3$)) of peracetylated derivative of varioxirane **16** agrees well with the data reported.[1] Upon treatment of varioxirane (**2**) with CSA in CH_2Cl_2 produced varitriol (**1**), which agrees with the proposed biosynthetic pathway.[1]

Compound (+)-**9** was needed for the synthesis of natural 2-methoxy-6-(3,4-dihydroxyhepta-1,5-dienyl)benzyl alcohol (**3**). Compound (+)-**9** could be derived from racemic (±)-**9** by using (+)-DIPT in the Sharpless kinetic resolution step as shown in the retrosynthetic analysis (Figure 2). However, the enantiomer of **3** could be derived from the unreacted allylic alcohol (−)-**9** obtained in the Sharpless kinetic resolution step of Scheme 1. Thus, compound (−)-**9**[11] (er 98.6:1.4, HPLC)[19] was silylated by using TBSOTf to give **17**, which was treated with lithiated methyl phosphonate to give *β*-ketophosphonate *ent*-**8** (R = TBS) in 95% yield over two steps (Scheme 4). Under HWE reaction conditions, *ent*-**8** was coupled with aldehyde **6** to yield the conjugated ketone *ent*-**5** in 82% yield. Desilylation of *ent*-**5** furnished **18** under the optimized conditions ($LiEt_3BH$, Et_2O, −78 °C) shown in Table 2 and provided *anti*-diol **19** as a major product (32:1) in favor of the desired isomer with 92% yield. Acetyl deprotection of **19** provided the anticipated *ent*-**3** in 85% yield. The spectral data and specific rotation of (−)-**3** ($[\alpha]^{30}_D$ = −36.0 (*c* 0.05, $CHCl_3$); natural product (+)-**3**:[7] $[\alpha]^{24}_D$ = +42.7 (*c* 0.22, $CHCl_3$)) are in good agreement with the data reported.[7]

In conclusion, a new synthetic route has been developed for varitriol based on the proposed biosynthetic pathway. En route to varitriol (**1**), the first total synthesis of varioxirane (**2**) was achieved. Additionally, the first total synthesis of an enantiomer of the proposed biosynthetic precursor, (1*E*,3*S*,4*R*,5*E*)-1-(2-(hydroxymethyl)-3-methoxyphenyl)hepta-1,5-diene-3,4-diol (*ent*-**3**), was also accomplished utilizing the same strategy and starting material. The first total synthesis reported herein for **2** and *ent*-**3** confirmed the absolute configuration of natural varioxirane and (1*E*,3*R*,4*S*,5*E*)-1-(2-(hydroxymethyl)-3-methoxyphenyl)hepta-1,5-diene-3,4-diol. Application of this strategy to other bioactive molecules and their analogues, in particular compounds related to **3**, is in progress in our laboratory, and it will be reported in due course.

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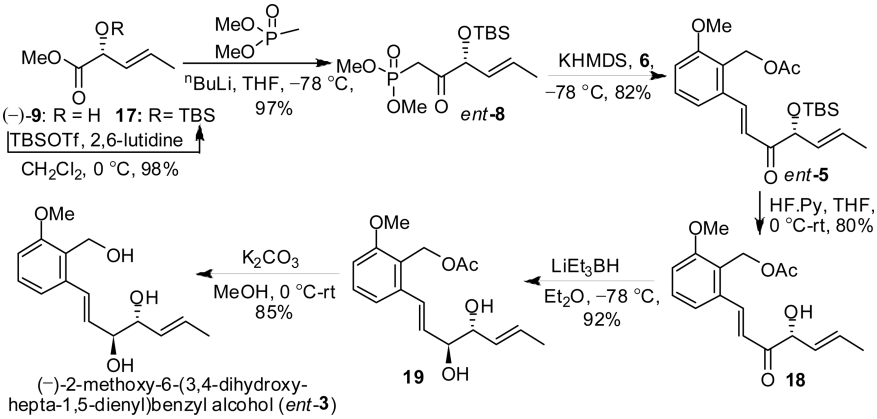
Scheme 4. Synthesis of *ent*-3



EXPERIMENTAL SECTION

(*E*)-Methyl 2-Hydroxypent-3-enoate ((±)-9).[10] Compound (*E*)-2-hydroxypent-3-enenitrile (3.535 g, 30%) was prepared as a colorless oil from (*E*)-but-2-enal (10.0 mL, 8.51 g, 121.5 mmol):[10a] R_f = 0.38 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (m, 1H), 5.58 (m, 1H), 4.90 (t, J = 6.0 Hz, 1H), 4.0 (br, 1H), 1.76 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.5, 124.7, 118.5, 61.3, 17.2; IR (neat) ν_{max} 3421, 2922, 2248, 1670, 1445, 1262, 1085 cm^{-1}; HRMS (EI) m/z [M]$^+$ calcd for $C_5H_7N_1O_1$ 97.0527, found 97.0527.

(*E*)-Methyl 2-hydroxypent-3-enoate ((±)-**9**) (4.3 g, 92%) was prepared from the above cyanohydrin (3.5 g, 36 mmol) as a colorless oil:[10b] R_f = 0.3 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (m, 1H), 5.49 (m, 1H), 4.56 (bs, 1H), 3.75 (s, 1H), 3.12 (bs, 1H), 1.69 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 129.4, 127.1, 71.2, 52.4, 17.4; IR (neat): ν_{max} 3450, 2922, 1737, 1440, 1214, 1139, 1049, 966 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_6H_{11}O_3$ 131.0703, found 131.0702.

(*S*)-Methyl 2-Hydroxy-2-((2*R*,3*R*)-3-methyloxiran-2-yl)-acetate (10). To a suspension of activated powdered 4A molecular sieves (1.3 g) in CH_2Cl_2 (70 mL) were added sequentially Ti(O^{i}Pr)$_4$ (4.92 mL, 16.5 mmol) and (−)-DIPT (4.08 mL, 19.8 mmol) at −20 °C. After the mixture was stirred for 30 min, TBHP (12.2 mL, 2.7 M in toluene, 33 mmol) was added and stirring continued for another 30 min at the same temperature. To the above solution was added compound (±)-**9** (4.3 g, 33 mmol) in CH_2Cl_2 (16 mL) and the resulting solution stirred for 8 h at −20 °C. The reaction mixture was quenched with water, warmed to rt, stirred for overnight, filtered, and concentrated under reduced pressure. The compound was extracted with EtOAc (2 × 200 mL), washed with brine, and dried over Na_2SO_4. The residue was purified by column chromatography (20% EtOAc/hexanes) to afford **10** (2.02 g, 42%) as a colorless oil: R_f = 0.3 (30% EtOAc/hexanes); $[\alpha]^{28}_D$ = +45.8 (c 0.27, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (t, J = 4.3 Hz, 1H), 3.82 (s, 3H), 3.11 (dq, J = 5.3, 2.0 Hz, 1H), 3.04 (d, J = 4.3 Hz, 1H), 2.97 (dd, J = 5.3, 2.0 Hz, 1H), 1.31 (d, J = 5.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 69.5, 58.7, 52.6, 51.5, 16.8; IR (neat) ν_{max} 3448, 2854, 1726, 1464, 1253, 1135, 1098, 1024, 835 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_6H_{11}O_4$ 147.0651, found 147.0651.

(*S*)-Methyl 2-(*tert*-Butyldimethylsilyloxy)-2-((2*S*,3*R*)-3-methyloxiran-2-yl)acetate (11). Compound **11** (3.42 g, 96%) was synthesized as a colorless oil from alcohol **10** (2 g, 13.7 mmol) following the general procedure for TBS protection described in ref 8a: R_f = 0.6 (10% EtOAc/hexanes); $[\alpha]^{28}_D$ = +3.59 (c 0.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (d, J = 3.7 Hz, 1H), 3.77 (s, 3H), 3.08 (qd, J = 5.3, 2.2 Hz, 1H), 3.01 (dd, J = 3.7, 2.2 Hz, 1H), 1.30 (d, J = 5.3 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 70.9, 59.1, 52.1, 50.9, 25.5, 18.2, 16.8, −5.3, −5.4; IR (neat) ν_{max} 2956, 2932, 2858, 1760, 1468, 1253, 1162, 839 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{12}H_{25}O_4Si$ 261.1516, found 261.1516.

2-Acetoxymethyl-3-methoxybenzaldehyde (6):[13] R_f = 0.4 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.23 (s, 1H), 7.46 (m, 2H), 7.14 (m, 1H), 5.51 (s, 2H), 3.86 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.7, 170.6, 158.3, 135.8, 130.1, 124.8, 122.7, 116.1, 56.0, 55.7, 20.7; IR (neat) ν_{max} 2922, 2851, 1730, 1691, 1586, 1468, 1362, 1223, 1023, 965 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{11}H_{12}O_4Na$ 231.0625, found 231.0627.

Dimethyl (*S*)-3-(*tert*-Butyldimethylsilyloxy)-3-((2*S*,3*R*)-3-methyloxiran-2-yl)-2-oxopropylphosphonate (7). Compound **7** (4.28 g, 93%) was synthesized from ester **11** (3.4 g, 13.1 mmol) as a highly viscous colorless oil following the procedure reported for β-ketophosphonate in ref 12: R_f = 0.3 (80% EtOAc/hexanes); $[\alpha]^{28}_D$ = +53.5 (c 0.71, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.18 (d, J = 4.2 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.45 (dd, J = 21.8, 15.1 Hz, 1H), 3.18 (dd, J = 21.8, 15.1 Hz, 1H), 3.0 (qd, J = 5.0, 2.5 Hz, 1H), 2.83 (dd, J = 4.2, 2.5 Hz, 1H), 1.30 (d, J = 5.0 Hz, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 77.5, 77.5, 58.7, 52.9, 52.8, 51.8, 36.7, 35.3, 25.6, 18.2, 16.9, −4.9, −5.1; IR (neat) ν_{max} 2855, 1727, 1465, 1254, 1153, 1029, 946, 839 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{30}O_6PSi$ 353.1541, found 353.1543.

2-((*S*,*E*)-4-(*tert*-Butyldimethylsilyloxy)-4-((2*S*,3*R*)-3-methyloxiran-2-yl)-3-oxobut-1-enyl)-6-methoxybenzyl Acetate (4). β-Ketophosphonate **7** (3.4 g, 9.65 mmol) was dissolved in THF (50 mL) and cooled to −78 °C. KHMDS (19.3 mL, 0.5 M in THF, 9.65 mmol) was added slowly. After 30 min at −78 °C, aldehyde **6** (3.01 g, 14.48 mmol) which dissolved in THF (30 mL) was added. After 1 h, the reaction mixture was warmed to rt and stirred for 24 h, the reaction was quenched by addition of aq NH_4Cl solution, and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The reaction mixture was purified by column chromatography on silica gel (8% EtOAc in hexanes) to give **4** (3.1 g, 74%) as a colorless oil: R_f = 0.5 (20% EtOAc/hexanes); $[\alpha]^{28}_D$ = −4.6 (c 0.86, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 16.0 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 7.18 (d, J = 16.0 Hz, 1H), 6.98 (d, J = 7.9 Hz, 1H), 5.33 (s, 2H), 4.36 (d, J = 3.4 Hz, 1H), 3.86 (s, 3H), 3.08 (qd, J = 5.3, 2.2 Hz, 1H), 2.95 (dd, J = 3.4, 2.2 Hz, 1H), 2.06 (s, 3H), 1.31 (d, J = 5.3 Hz, 3H), 0.93 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 170.5, 158.3, 140.7, 136.3, 129.9, 123.6, 123.5, 118.7, 112.3, 76.7, 59.3, 56.9, 55.7, 50.8, 25.5, 20.7, 18.1, 16.8, −5.1, −5.2; IR (neat) ν_{max} 2925, 2853, 1737, 1690, 1609, 1576, 1470, 1379, 1361, 1258, 1224, 1130, 1097, 1023, 951, 838, 673 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{23}H_{35}O_6Si$ 435.2198, found 435.2197.

2-((3*S*,4*R*,*E*)-4-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-4-((2*S*,3*R*)-3-methyloxiran-2-yl)but-1-enyl)-6-methoxybenzyl acetate (12a). Compound **12a** (45 mg, 90%) was synthesized as a colorless oil from compound **4** (50 mg, 0.115 mmol) following the procedure described in ref 17: R_f = 0.3 (30% EtOAc/hexanes); $[\alpha]^{28}_D$ = +21.4 (c 0.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, J = 8.3 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 15.8 Hz, 1H), 6.83

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(d, J = 8.3 Hz, 1H), 6.19 (dd, J = 15.8,5.7 Hz, 1H), 5.27 (s, 2H), 4.36 (ddd, J = 5.7, 3.8, 1.5 Hz, 1H), 3.83 (s, 3H), 3.51 (dd, J = 5.8, 3.8 Hz, 1H), 2.96 (dd, J = 5.3, 2.1 Hz, 1H), 2.82 (dd, J = 5.8, 2.1 Hz, 1H), 2.06 (s, 3H), 1.33 (d, J = 5.3 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 158.4, 138.9, 132.5, 129.8, 127.9, 121.1, 118.5, 109.8, 74.8, 73.8, 59.1, 57.6, 55.7, 53.3, 25.7, 21.0, 18.1, 17.2, −4.4, −4.8; IR (neat) ν_{max} 3451, 2924, 2853, 1734, 1579, 1470, 1380, 1360, 1251, 1100, 1023, 836 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{23}H_{36}O_6NaSi$ 459.2157, found 459.2173.

Synthesis of A and A1. Column-separable **A** and **A1** (1:2) (110 mg, 92%) were prepared from the mixture **12** and **12a** (120 mg, 0.275 mmol) following the same procedure described in ref 8a.

Data of A (minor): R_f = 0.3 (30% EtOAc/hexanes); $[\alpha]^{26}_D$ = +25.26 (c 0.77, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (t, J = 7.9 Hz, 1H), 7.13 (d, J = 7.9 Hz, 1H), 6.94 (d, J = 15.7 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.09 (dd, J = 15.7, 8.0 Hz, 1H), 5.25 (s, 2H), 4.29 (m, 1H), 3.97 (t, J = 5.5 Hz, 1H), 3.89 (t, J = 5.5 Hz, 1H), 3.84 (s, 3H), 3.63 (m, 1H), 2.67 (d, J = 5.5 Hz, 1H), 2.05 (s, 3H), 1.34 (d, J = 6.4 Hz, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 158.4, 138.5, 130.8, 129.9, 129.6, 118.6, 110.0, 84.5, 79.8, 76.7, 76.2, 57.6, 55.8, 25.7, 21.0, 18.9, 18.0, −4.3, −4.9; IR (neat) ν_{max} 3450.9, 2925.9, 2854.4, 1733.3, 1579.9, 1467.7, 1381.6, 1253.9, 1103.4, 1023.0, 964.5, 774.1 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{36}O_6NaSi$ [M + Na]$^+$ 439.2175, found 439.2173.

Data of A1 (major): $[\alpha]^{28}_D$ = +38.02 (c 0.40, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, J = 7.9 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.81 (d, J = 15.8 Hz, 1H), 6.28 (dd, J = 15.8, 8.0 Hz, 1H), 5.26 (ABq, J = 16.3, 11.6 Hz, 2H), 4.62 (m, 1H), 4.30 (t, J = 5.0 Hz, 1H), 3.98 (m, 1H), 3.84 (s, 3H), 3.74 (m, 1H), 2.34 (d, J = 8.3 Hz, 1H), 2.06 (s, 3H), 1.32 (d, J = 6.4 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 158.4, 138.4, 129.7, 129.5, 121.1, 118.4, 109.8, 81.5, 78.3, 77.9, 74.7, 57.5, 55.8, 25.7, 21.0, 18.8, 18.2, −4.5, −4.9; IR (neat) ν_{max} 3448.6, 2928.0, 2855.5, 1733.6, 1579.9, 1468.8, 1380.9, 1257.4, 1083.4, 967.9, 839 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{36}O_6NaSi$ [M + Na]$^+$ 439.2159, found 439.2173.

Synthesis of 1 and 1a. Independently, **1** (14.5 mg, 82%) and **1a** (27.0 mg, 81%) were synthesized from **A** (37 mg, 0.085 mmol) and **A1** (70 mg, 0.160 mmol), respectively, by following the procedures described for deprotection of silyl and acetyl reported in ref 8a.

Data of 1a: R_f = 0.3 (EtOAc); $[\alpha]^{28}_D$ = +6.23 (c 1.38, CH_3OH); ^{1}H NMR (500 MHz, CD_3CN) δ 7.24 (t, J = 7.9 Hz, 1H), 7.14 (d, J = 7.9 Hz, 1H), 6.96 (d, J = 15.8 Hz, 1H), 6.89 (d, J = 7.9 Hz, 1H), 6.24 (dd, J = 15.8, 7.1 Hz, 1H), 4.66 (d, J = 5.0 Hz, 2H), 4.59 (m, 1H), 4.08 (m, 1H), 3.87 (m, 1H), 3.82 (s, 3H), 3.75 (m, 1H), 3.32 (bd, J = 3.9 Hz, 1H), 3.25 (bd, J = 7.3 Hz, 1H) 2.94 (t, J = 3.9 Hz, 1H), 1.23 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 158.4, 138.4, 130.1, 129.4, 129.2, 127.0, 119.0, 110.3, 81.3, 78.6, 77.7, 74.1, 55.8, 55.1, 18.7; IR (neat) ν_{max} 3381.5, 2924.7, 2854.7, 1578.5, 1470.8, 1375.7, 1265.1, 1135.0, 1075.2, 1016.4, 975.3, 784.8; HRMS (ESI) calcd for $C_{15}H_{20}O_5Na$ [M + Na]$^+$ 303.1197, found 303.1202.

2-((*S*,*E*)-4-Hydroxy-4-((2*R*,3*R*)-3-methyloxiran-2-yl)-3-oxo-but-1-enyl)-6-methoxybenzyl Acetate (13). Compound **13** (1.84 g, 81%) was synthesized as a solid from **4** (3.1 g, 7.1 mmol) following the TBS deprotection reported in ref 2k: R_f = 0.3 (40% EtOAc/hexanes); mp 110−112 °C; $[\alpha]^{28}_D$ = +23.3 (c 0.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 16.0 Hz, 1H), 7.37 (t, J = 7.8, Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.00 (d, J = 16.0 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 5.35 (ABq, J = 12 Hz, 2H), 4.07 (d, J = 7.6 Hz, 1H), 3.87 (s, 3H), 3.17 (qd, J = 5.3, 2.0 Hz, 1H), 2.70 (dd, J = 7.6, 2.0 Hz, 1H), 2.06 (s, 3H), 1.38 (d, J = 5.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 170.9, 158.6, 143.1, 135.8, 130.1, 124.0, 123.8, 119.1, 112.9, 76.6, 58.3, 57.0, 55.9, 54.2, 20.9, 17.1; IR (neat) ν_{max} 3450, 2923, 2851, 1733, 1689, 1610, 1576, 1472, 1440, 1379, 1260, 1099, 1081, 1023, 633 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{17}H_{20}O_6Na$ 343.1150, found 343.1152.

2-((3*R*,4*R*,*E*)-3,4-Dihydroxy-4-((2*R*,3*R*)-3-methyloxiran-2-yl)-but-1-enyl)-6-methoxybenzyl Acetate (14). To a solution of ketone **13** (1.2 g, 3.7 mmol) in ether (20 mL) was slowly added $LiEt_3BH$ (5.6 mL, 1.0 M in THF, 5.6 mmol) at −78 °C. After the mixture was stirred for 10 min at −78 °C, the reaction mixture was quenched with H_2O. This mixture was extracted with EtOAc, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (50% EtOAc/hexanes) to afford diol **14** (977 mg, 82%) as colorless oil: R_f = 0.2 (70% EtOAc/hexanes); $[\alpha]^{28}_D$ = +10.0 (c 0.24, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, J = 8.0 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.00 (d, J = 16.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.22 (dd, J = 16.0, 7.0 Hz, 1H), 5.29 (ABq, J = 12.0 Hz, 2H), 4.49 (dd, J = 7.0, 6.0 Hz, 1H), 3.85 (s, 3H), 3.81 (dd, J = 6.0, 5.0 Hz, 1H), 3.11 (m, 1H), 2.86 (dd, J = 5.0, 3.0 Hz, 1H), 2.45 (bs, 1H), 2.38 (bs, 1H), 2.05 (s, 3H), 1.32 (d, J = 5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 158.5, 138.7, 130.6, 130.0, 129.7, 121.3, 118.9, 110.1, 73.9, 72.2, 61.5, 58.6, 57.6, 55.8, 51.9, 21.1, 17.1; IR (neat) ν_{max} 3451, 3377, 2921, 2852, 1734, 1579, 1461, 1378, 1220, 1023, 965 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{17}H_{22}O_6Na$ 345.1309, found 345.1308.

2-((*E*)-2-((2*R*,3*S*,4*R*,5*S*)-3,4-Dihydroxy-5-methyltetrahydrofuran-2-yl)vinyl)-6-methoxybenzyl Acetate (15). Compound **15** (37 mg, 93%) was synthesized as a liquid from epoxide **14** (40 mg, 0.124 mmol) following the same procedure described for epoxide opening in ref 8a: R_f = 0.3 (70% EtOAc/hexanes); $[\alpha]^{28}_D$ = +20.8 (c 0.56, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (t, J = 8.3 Hz, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.98 (d, J = 15.7 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.10 (dd, J = 15.7, 7.0 Hz, 1H), 5.29 (ABq, J = 11.5 Hz, 2H), 4.33 (t, J = 7.0 Hz, 1H), 3.94 (m, 2H), 3.84 (s, 3H), 3.79 (t, J = 5.5 Hz, 1H), 2.05 (s, 3H), 1.35 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ158.5, 138.8, 131.2, 129.9, 129.5, 121.2, 118.9, 110.0, 84.0, 80.0, 76.2, 75.4, 57.6, 55.8, 21.1, 19.1; IR (neat) ν_{max} 3428, 2921, 2851, 1733, 1580, 1462, 1379, 1266, 1078, 966 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{17}H_{22}O_6Na$ 345.1308, found 345.1308.

Varitriol (1). (+)-Varitriol (**1**) (15.3 mg, 88%) was synthesized as a solid from compound **15** (20 mg, 0.062 mmol) following the acetyl deprotection reported in ref 8a: R_f = 0.3 (EtOAc); $[\alpha]^{30}_D$ = +23.8 (c 0.26, CH_3OH); ^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.23 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 15.8 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.21 (dd, J = 15.8, 6.7 Hz, 1H), 4.72 (s, 2H), 4.29 (t, J = 6.7 Hz, 1H), 4.23 (brs, 1H), 4.03 (brs, 1H), 3.91 (m, 1H), 3.84 (m, 1H), 3.83 (s, 3H), 3.70 (m, 1H), 3.65 (brs, 1H), 1.28 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 158.9, 139.0, 132.4, 129.4, 129.3, 128.0, 119.3, 110.6, 85.3, 80.0, 77.2, 76.5, 56.0, 55.5, 19.5; IR (neat) ν_{max} 3355, 2920, 1578, 1354, 1219, 1088; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{15}H_{20}O_5Na$ 303.1199, found 303.1202.

Varioxirane (2). Compound **2** (70 mg, 81%) was synthesized as a liquid from compound **14** (100 mg, 0.31 mmol) following the same procedure described in ref 8a: R_f = 0.3 (EtOAc); $[\alpha]^{30}_D$ = −24.61 (c 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.4 Hz, 1H), 7.25 (d, J = 15.9 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.21 (dd, J = 15.9, 6.7 Hz, 1H), 4.80 (s, 2H), 4.50 (dd, J = 6.7, 4.2 Hz, 1H), 3.86 (s, 3H), 3.81 (t, J = 4.2 Hz, 1H), 3.10 (qd, J = 5.0, 2.5 Hz, 1H), 2.86 (dd, J = 4.2, 2.5 Hz, 1H), 2.55 (brs, 1H), 1.70 (bs, 2H), 1.31 (d, J = 5.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 137.7, 130.5, 129.3, 128.9, 125.9, 119.1, 109.7, 73.8, 72.7, 58.7, 55.8, 55.6, 52.3, 17.1; IR (neat) ν_{max} 3454, 3376, 2923, 2853, 1577, 1469, 1260, 1074, 998 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{15}H_{20}O_5Na$ 303.1204, found 303.1202.

Triacetylvarioxirane (16). Compound **16** (42 mg, 95%) was synthesized as a colorless oil from compound **2** (30 mg, 0.11 mmol), Ac_2O (0.04 mL, 0.42 mmol), and Et_3N (0.09 mL, 0.64 mmol) following the same procedure described for acetyl in ref 8a: R_f = 0.5 (30% EtOAc/hexanes); $[\alpha]^{30}_D$ = −32.9 (c 0.19, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (t, J = 8.3 Hz, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.98 (d, J = 15.8 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 6.14 (dd, J = 15.8, 7.5 Hz, 1H), 5.70 (ddd, J = 7.5, 3.7, 1.5 Hz, 1H), 5.26 (s, 2H), 4.90 (dd, J = 6.0, 3.7 Hz, 1H), 3.84 (s, 3H), 3.03 (dq, J = 5.3, 2.2 Hz, 1H), 2.85 (dd, J = 6.0, 2.2 Hz, 1H), 2.12 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 1.30 (d, J = 5.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 169.8, 169.7, 158.4, 138.2, 131.9, 131.7, 129.9, 125.8, 118.8, 110.4, 73.7, 73.1, 57.5, 55.9, 55.8, 52.9, 21.0, 20.9, 20.8, 17.1; IR (neat) ν_{max} 2922, 2851, 1741, 1579, 1469,1373,1224,1024 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{21}H_{26}O_8Na$ 429.1503, found 429.1519.

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Varitriol (1). Varitriol (**1**) (18.2 mg, 91%) was synthesized from varioxirane (**2**) (20 mg, 0.07 mmol) following the same procedure described in ref 8a.

(*R*,*E*)-Methyl 2-Hydroxypent-3-enoate ((−)-9). Compound (−)-**9** (1.2 g, 24%) was obtained from (±)-**9** (5 g, 38.46 mmol) following the same procedure described for **10**: R_f = 0.6 (30% EtOAc/hexanes); $[\alpha]^{30}_D$ = −96.4 (*c* 0.09, $CHCl_3$);

(*R*,*E*)-Methyl 2-(*tert*-Butyldimethylsilyloxy)pent-3-enoate (17). Compound **17** (3.677 g, 98%) was synthesized as a colorless oil from (−)-**9** (2 g, 15.38 mmol) following the same procedure described in ref 8a: R_f = 0.7 (10% EtOAc/hexanes); $[\alpha]^{28}_D$ = +3.9 (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.56 (qdd, *J* = 15.2, 5.7, 1.6 Hz, 1H), 4.64 (m, 1H), 3.71 (s, 3H), 1.70 (dt, *J* = 6.6, 1.6 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 128.2, 128.2, 73.1, 51.9, 25.6, 18.3, 17.5, −5.1, −5.2; IR (neat) ν_{max} 2929, 2857, 1758, 1436, 1253, 1153, 1062, 965, 835 cm^{-1}; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{25}O_3Si$ 245.1562, found 245.1567.

(*R*,*E*)-Dimethyl 3-(*tert*-Butyldimethylsilyloxy)-2-oxohex-4-enylphosphonate *ent*-(8). Compound *ent*-**8** (4.673 g, 97%) was synthesized as a highly viscous colorless oil from ester **17** (3.5 g, 14.34 mmol) following the same procedure described in ref 12: R_f = 0.3 (70% EtOAc/hexanes); $[\alpha]^{28}_D$ = +4.97 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.38 (ddd, *J* = 15.0, 6.3,1.6 Hz, 1H), 4.53(d, *J* = 6.3 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.32−3.10 (m, 2H), 1.69 (d, *J* = 6.3 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 201.2, 130.1, 127.4, 80.0, 79.9, 52.9, 52.8, 52.7, 35.3, 33.5, 25.6, 18.1, 17.7, −4.7, −5.1; IR (neat) ν_{max} 2955, 2857, 1727, 1682, 1467, 1389, 1257, 1034, 968, 839 cm^{-1}; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{30}O_5$ PSi 337.1586, found 337.1594.

2-((*R*,1*E*,5*E*)-4-(*tert*-Butyldimethylsilyloxy)-3-oxohepta-1,5-dienyl)-6-methoxybenzyl Acetate *ent*-(5). Compound *ent*-**5** (4.589 g, 82%) was synthesized as a solid from *β*-ketophosphonate *ent*-**8** (4.5 g, 13.39 mmol) and aldehyde **6** (4.178 g, 20.08 mmol) following the same procedure described for **4**: R_f = 0.5 (20% EtOAc/hexanes); mp 70−72 °C; $[\alpha]^{31}_D$ = −93.7 (*c* 0.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 15.9 Hz, 1H), 7.34 (t, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.08 (d, *J* = 15.9 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 5.90 (dqd, *J* = 15.2, 6.7, 1.6 Hz, 1H), 5.50 (qdd, *J* = 15.2, 5.5, 1.6 Hz, 1H), 5.30 (ABq, *J* = 12.0 Hz, 2H), 4.65 (m, 1H), 3.84 (s, 3H), 2.03 (s, 3H), 1.71 (td, *J* = 6.7, 1.6 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 170.7, 158.4, 140.3, 136.8, 129.9, 128.6, 128.4, 123.8, 123.4, 118.9, 112.2, 79.5, 57.1, 55.8, 25.7, 20.8, 18.2, 17.7, −4.8, −5.0; IR (neat) ν_{max} 2929, 2855, 1737, 1693, 1575, 1470, 1379, 1257, 1096, 964, 884, 674 cm^{-1}; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{35}O_5Si$ 419.2235, found 419.2248.

2-((*R*,1*E*,5*E*)-4-Hydroxy-3-oxohepta-1,5-dienyl)-6-methoxybenzyl Acetate (18). Compound **18** (680 mg, 80%) was synthesized as a liquid from compound **5** (1.2 g, 2.8 mmol) following the same procedure described in ref 2k: R_f = 0.4 (40% EtOAc/hexanes); $[\alpha]^{30}_D$ = −128.7 (*c* 0.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 15.8 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 15.8 Hz, 1H), 6.0 (qd, *J* = 15.1, 6.7 Hz, 1H), 5.45 (qdd, *J* = 15.1, 7.7, 1.6 Hz, 1H), 5.32 (s, 2H), 4.82 (d, *J* = 7.7, 1H), 3.87 (s, 3H), 2.06 (s, 3H), 1.78 (dd, *J* = 6.7, 1.6 Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 170.7, 158.5, 149.0, 141.6, 136.5, 132.1, 130.0, 127.4, 123.6, 118.9, 112.7, 77.4, 57.0, 55.8, 20.8, 17.9; IR (neat) ν_{max} 3451, 2928, 2850, 1737, 1692, 1575, 1440, 1250, 1127, 1004, 915, 830; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{20}O_5Na$ 327.1195, found 327.1202.

2-((1*E*,3*S*,4*R*,5*E*)-3,4-Dihydroxyhepta-1,5-dienyl)-6-methoxybenzyl Acetate (19). Compound **19** (182 mg, 92%) was synthesized as a colorless oil from ketone **18** (200 mg, 0.65 mmol) following the same procedure described for **14**: R_f = 0.3 (60% EtOAc/hexanes); $[\alpha]^{30}_D$ = −96.6 (*c* 0.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.93 (d, *J* = 15.8 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.12 (dd, *J* = 15.8, 6.4 Hz, 1H), 5.82 (qd, *J* = 15.3, 6.4 Hz, 1H), 5.54 (dd, *J* = 15.3, 7.0 Hz 1H), 5.28 (ABq, *J* = 12.0 Hz, 2H), 4.30 (m, 1H), 4.18 (m, 1H), 3.84 (s, 3H), 2.33 (brs, 1H), 2.18 (brs, 1H), 2.06 (s, 1H), 1.74 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 158.5, 139.0, 131.2, 130.1, 129.9, 129.7, 128.9, 121.2, 118.9, 110.0, 75.6, 75.4, 57.7, 55.8, 21.1, 17.9; IR (neat) ν_{max} 3426, 2921, 2852, 1730, 1579, 1470, 1379, 1250, 1079, 1022, 963 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{22}O_5Na$ 329.1361, found 329.1359.

(1*E*,3*S*,4*R*,5*E*)-1-(2-(Hydroxymethyl)-3-methoxyphenyl)-hepta-1,5-diene-3,4-diol (*ent*-3). Compound *ent*-**3** (58 mg, 85%) was synthesized as a liquid from compound **19** (80 mg, 0.26 mmol) following the same procedure described in ref 8a: R_f = 0.3 (EtOAc); $[\alpha]^{30}_D$ = −36.0 (*c* 0.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 16.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.06 (dd, *J* = 16.0, 4.5 Hz, 1H), 5.74 (dq, *J* = 15.2, 6.4 Hz, 1H), 5.48 (dd, *J* = 15.2, 4.5 Hz, 1H), 4.73 (ABq, *J* = 12.0 Hz, 2H), 4.24 (t, *J* = 6.4 Hz, 1H), 4.12 (m, 1H), 3.80 (s, 3H), 2.60 (brs, 2H), 1.67 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 139.2, 132.6, 131.2,130.9, 130.4, 130.2, 127.4, 120.6, 110.0, 76.9, 76.7, 57.7, 57.0, 19.2; IR (neat) ν_{max} 3380, 2919, 1577, 1471, 1381, 1261, 1079, 969 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}O_4Na$ 287.1249, found 287.1253.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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