From the overstem bark roots of *Orthosphenia mexicana* Standley (Celastraceae) was obtained a methanolic extract (13 g). After chromatography over silica gel, two major components, celastrol (**9**, 0.9 g) and orthosphenic acid (**1**, 300 mg), were isolated.

Orthosphenic Acid (1). This pale yellow compound had the following: mp 298–300 and 330 °C (double); IR (KBr) 3520–2800, 3210, 2980, 2950, 2920, 2900, 2875, 1695, 1450, 1438, 1390, 1240, 1210, 1190, 1145, 1065, 955 cm^{-1}; ^1H NMR (C_5D_5N) δ 0.85 (s, 3 H),0.92 (s, 3 H), 1.15 (br s, 9 H), 1.22 (s, 3 H), 3.74 (d, 1 H, J = 9 Hz), 4.22 (d, 1 H, J = 9 Hz), 4.35 (br s, 1 H, $W_{1/2}$ = 8 Hz) (partially overlapping with doublet at 4.22); mass spectrum, m/z (relative intensity) 488 (M^+, 20), 412 (32.9), 189 (28.6), 163 (15.0), 161 (16.0), 155 (20.8), 149 (21.6), 147 (16.9), 135 (21.7), 133 (17.3), 125 (99.1), 123 (19.5), 122 (18.7), 121 (34.2), 119 (33.3), 109 (100.0); calcd for $C_{30}H_{48}O_5$ mol wt 488.3501, found mol wt 488.3525 (high-resolution mass spectroscopy).

Methyl Orthosphenate (2). Esterification of **1** (20 mg) with diazomethane yielded **2**: mp 258–260 °C; IR (KBr) 3495, 3300, 2920, 2860, 1760, 1500, 1375, 1255, 1215, 1185, 1150, 1135, 1060, 1050, 980, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (s, 6 H), 0.91 (d, 3 H, J = 9 Hz), 0.93 (s, 3 H), 1.06 (s, 3 H), 1.16 (s, 3 H), 3.57 (d, 1 H, J = 9 Hz) (partially overlapping with singlet at 3.63) 3.63 (s, 3 H), 3.86 (br s, 1 H, $W_{1/2}$ = 8 Hz), 4.08 (d, 1 H, J = 9 Hz); mass spectrum, m/z (relative intensity) 5.02 (M^+, 26.4), 169 (28.3), 163 (12.2), 125 (100), 121 (24.1), 109 (39.3); calcd for $C_{31}H_{50}O_5$ mol wt 502.3658, found mol wt 502.3660 (high-resolution mass spectroscopy).

Monoacetate of Orthosphenic Acid (3). Esterification of **1** (25 mg) with acetic anhydride in pyridine at room temperature for 4 h yielded 12 mg of **3** and 11 mg of **5**. Compound **3** had the following: mp 250–252 C; IR (KBr) 3650–3100, 2920, 1740, 1450, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 3 H), between 0.91 (s), 0.95 (s), and 0.98 (s) (12 H), 2.10 (s, 3 H), 3.64 (d, 1 H, J = 9 Hz), 4.12 (d, 1 H, J = 9 Hz), 5.04 (br s, 1 H, $W_{1/2}$ = 9 Hz); mass spectrum, m/z (relative intensity) 530 (M^+, 64.0), 412 (32.0), 235 (6.0), 189 (52.0), 163 (89.0), 161 (4.0), 155 (10.0), 149 (62.0), 135 (6.2), 125 (100.0), 121 (113.0), 112 (4.7), 109 (10.0), 105 (64.0), 95 (18.4); calcd for $C_{32}H_{50}O_6$ mol wt 530.3607, found mol wt 530.3619 (high-resolution mass spectroscopy).

Monoacetate of Methyl Orthosphenate (4). Compound **3** (12 mg) was suspended in ethyl ether and esterified with diazomethane, yielding 11 mg of **4**: mp 232–234 °C; IR (KBr) 3420, 2910, 2850, 1740, 1720, 1450, 1380, 1370, 1250, 1220, 1135, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (s, 6 H), 0.93 (s, 3 H), 0.94 (d, 3 H, J = 8 Hz), 1.06 (s, 3 H), 1.17 (s, 3 H), 2.10 (s, 3 H), 3.62 (d, 1 H, J = 9 Hz), 3.64 (s, 3 H), 4.10 (d, 1 H, J = 9 Hz), 5.02 (br s, 1 H, $W_{1/2}$ = 9 Hz); mass spectrum, m/z (relative intensity) 544 (M^+); calcd for $C_{33}H_{52}O_6$ mol wt 544.3764, found mol wt 544.3787 (high-resolution mass spectroscopy).

Diacetate of Orthosphenic Acid (5). This compound had the following: mp 106–110 °C; IR (KBr) 3600–3000, 2920, 2860, 1730, 1450, 1380, 1250, 1230, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ (0.84 (d, 3 H, J = 7 Hz), 0.86 (s, 3 H), 0.96 (s) and 0.98 (s) (9 H), 1.09 (s, 3 H), 1.99 (s, 3 H), 2.07 (s, 3 H), 3.74 (d, 1 H, J = 9 Hz), 4.27 (d, 1 H, J = 9 Hz), 5.85 (br s, 1 H, $W_{1/2}$ = 9 Hz); mass spectrum, m/z (relative intensity) 530 (M^+ – 42) (73.4), 412 (4.6), 383 (5.5), 373 (4.2), 259 (4.8), 235 (9.7), 189 (5.5), 163 (9.1), 155 (7.6), 149 (6.6), 147 (5.1), 135 (7.1), 133 (5.7), 125 (100.0), 121 (12.7), 109 (21.6), 95 (21.4); calcd for $C_{32}H_{50}O_6$ (M^+ – 42) mol wt 530.3607, found mol wt 530.3589 (high-resolution mass spectroscopy).

Diacetate of Methyl Orthosphenate (6). Esterification of **5** (11 mg) with diazomethane yielded 10 mg of **6**: mp 144–146 °C; IR (KBr) 2910, 1860, 1750, 1730, 1460, 1450, 1380, 1370, 1250, 1220, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (s, 6 H), 0.92 (s, 3 H), 0.93 (d, 3 H, J = 9 Hz), 1.06 (s, 3 H), 1.16 (s, 3 H), 1.98 (s, 3 H), 2.07 (s, 3 H), 3.64 (s, 3 H), 3.72 (d, 1 H, J = 11 Hz), 4.27 (d, 1 H, J = 11 Hz); mass spectrum, m/z 586 (M^+); calcd for $C_{32}H_{50}O_6$ (M^+ – 42) mol wt 544.3764, found mol wt 544.3761 (high-resolution mass spectroscopy).

Acetonide of Methyl Orthosphenate (7). This compound was obtained by refluxing **2** (20 mg) in dry acetone and copper sulfate, yielding 18 mg of **7**: mp 228–230 °C; IR (KBr) 2910, 2860, 1720, 1380, 1190, 1160, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 6 H), 0.94 (d, 3 H, J = 8 Hz), 0.96 (s, 3 H), 1.08 (s, 3 H), 1.18 (s, 3 H), 2.76 (s, 2 H), 3.63 (d, 1 H, J = 9 Hz), 3.66 (s, 3 H), 3.90 (br s, 1 H, $W_{1/2}$ = 9 Hz), 4.13 (d, 1 H, J = 9 Hz); mass spectrum, m/z (relative intensity) 502 (M^+ – 40, 33.7), 319 (6.0), 249 (7.3), 189 (8.0), 169 (28.8), 163 (11.1), 149 (71.0), 135 (9.2), 125 (100.0), 109 (34.1), 95 (24.6); calcd for $C_{31}H_{50}O_5$ (M^+ - 40) mol wt 502.3658, found mol wt 502.3665 (high-resolution mass spectroscopy).

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Registry No. 1, 86632-20-4; 2, 86632-21-5; 3, 86632-22-6; 4, 86632-24-8; 5, 86632-23-7; 6, 86632-25-9; 7, 86632-26-0; 8, 34157-83-0.

Total Synthesis of (–)-Vertinolide. A General Approach to Chiral Tetronic Acids and Butenolides from Allylic Alcohols†

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A new method for the synthesis of chiral tetronic acids and butenolides from achiral allylic alcohols is described. Asymmetric epoxidation, followed by a one-step epoxide isomerization and opening under conditions of heating with NaCN, furnishes β-hydroxybutyrolactones upon acidic workup. These alcohols can either be dehydrated to the corresponding optically active α,β-unsaturated butyrolactones or oxidized in Me_2SO–trifluoroacetic anhydride to chiral tetronic acids. To illustrate the method, a chiral synthesis of vertinolide (**3**), a tetronic acid of fungal origin, is described which for the first time establishes this metabolite's absolute configuration.

Chiral, 4-substituted butenolides are natural products of considerable interest to man as ecologically important pheromones,[1] flavoring components in fruit and other foods,[2] and potent mycotoxins.[3] Tetronic acids comprise a subclass of β-hydroxybutenolides with general structure **1**, perhaps the best known of which is ascorbic acid (**2**) (vitamin C). Many tetronic acids and their derivatives

† Dedicated to the memory of the late Professor Daniel Swern.

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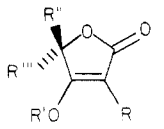
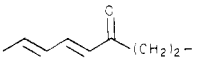


1, R, R', R'', R''' = H
2, R = OH; R', R''' = H; R'' = CH(OH)CH$_2$OH

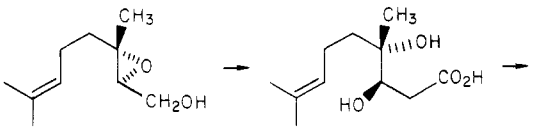


3, R, R'' = CH$_3$; R' = H; R''' =

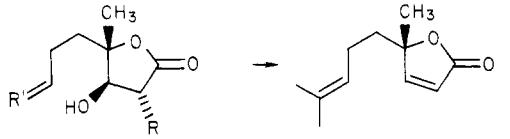
possess noteworthy antibiotic, insecticidal, and herbicidal properties.[4]

To date the synthesis of such compounds in optically pure form has been achieved by standard resolution,[5] kinetic resolution using enzymes,[6] selection of a chiral starting material,[7] or, most recently, enantioselective reduction of α-acetylenic ketones.[8,9] Unfortunately, even this last approach is not directly applicable to highly branched tetronic acids such as vertinolide (**3**), a new mycotoxin from *Verticillium intertextum*.[10] Although knowledge of vertinolide's absolute configuration is of importance in understanding its most unusual biosynthesis,[10,11] all efforts to obtain this information conclusively from degradation, chiral synthesis, chiroptical studies, or X-ray crystallographic analysis have thus far failed.[11] To address this problem we have devised an unusual epoxide alkylation and a new oxidation of β-hydroxy lactones, which together constitute a three-step construction of optically active tetronic acids and butenolides from achiral allylic alcohols. We now report the enantioselective total synthesis of (−)-**3** in eight steps from 2(*S*),3(*S*)-geranyl oxide (**4**),[12] thus establishing the *S* configuration for naturally-occurring vertinolide, as well as the power of the method.

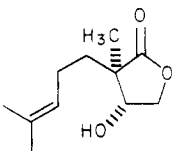
When **4** was heated with NaCN (14 equiv, 6.5 M in 1:2 EtOH:H$_2$O, reflux, 5.5 h), a mixture of dihydroxy acids (80%) containing mostly **5** was produced as a result of the facile epoxy alcohol equilibrium described by Payne.[13] Lactonization (*p*-TsOH, C_6H_6, reflux, 1 h) of the crude product furnished virtually pure levorotatory butyrolactone **6** in nearly 40% yield from **4**.[14] From chromatographies of large-scale experiments it was also possible to isolate 3–4% of a less polar lactone **7** arising from direct displacement by cyanide at C3 of **4**. Lactone **6** was readily dehydrated (MsCl, Et_3N, 0, °C → room temperature, 90%) to butenolide **8**, which was easily identified by its characteristic NMR absorptions.



4 **5**



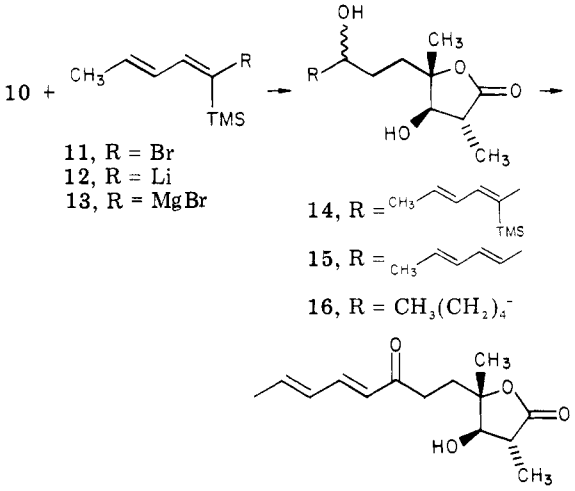
6, R = H; R' = C(CH$_3$)$_2$
9, R = CH$_3$; R' = C(CH$_3$)$_2$
10, R = CH$_3$; R' = O



7

Alkylation of the dianion of **6** with methyl iodide[15] (LiICA, THF–HMPA) furnished exclusively **9** in 89% yield. Careful ozonolysis followed by reductive workup afforded aldehyde **10** in 82–91% yield after flash column chromatography.

The assembly of vertinolide's carbon framework was completed by joining aldehyde **10** with (*E*,*E*)-1-bromo-1-(trimethylsilyl)penta-1,3-diene (**11**)[16] as follows. Met-



11, R = Br
12, R = Li
13, R = MgBr

14, R =
15, R =
16, R = CH$_3$(CH$_2$)$_4$

17

al-halogen exchange between equimolar quantities of **11** and *sec*-BuLi (THF–cyclohexane, −78 °C, 30 min)[19] followed by the addition of anhydrous $MgBr_2$ (1.25 equiv, freshly prepared by the reaction of Mg with $BrCH_2CH_2Br$ in 3:1 ether:benzene)[20] to the intermediate lithiated species **12** produced the alkenyl Grignard reagent **13**. Aldehyde **10** was then injected by syringe into a solution of **13** (5 equiv, −78 °C) to furnish adduct(s) **14** in 66% yield.[21]

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(21) Direct condensation of **12** or of *trans,trans*-1,3-pentadienyllithium with **10** furnished adducts irreproducibly and in low yield. Even with **13**, enolization of **10** persisted as a minor side reaction.

Protiodesilylation[22] of **14** ($(Bu)_4NF$ in THF, 45 °C) gave **15** (70%), which was best oxidized in two separate stages to vertinolide. First, MnO_2 in CH_2Cl_2 transformed **15** to enone **17** in 73% yield. Oxidation of the hindered ring hydroxyl in **17** and its congeners **6**, **7**, and **9** proved difficult, and the forcing conditions required by many transition-metal oxide reagents led to retroaldol fragmentation, β-elimination, and other byproducts of overoxidation. However superior results were achieved by using Swern's reagent (Me_2SO–trifluoroacetic anhydride),[23] with which **17** could be converted into pure **3** in 80% yield. Lactones **6**, **7**, **9**, and **16**[24] were all oxidized in similar fashion to the corresponding enolic products in 70–80% yields, leading us to recommend this reagent for the formation of highly functionalized tetronic acids.[25] Synthetic vertinolide was identical in all respects with an authentic sample of the levorotatory natural product and must therefore possess the absolute configuration depicted in **3**.

Experimental Section

General. "Dry" solvents and reagents were distilled prior to use. THF, ether, and benzene were distilled under a N_2 atmosphere from sodium-benzophenone solutions. Triethylamine, CH_2Cl_2, and Me_3SiCl were distilled from CaH_2 under N_2. Isopropylcyclohexylamine and HMPA were fractionally distilled from CaH_2 at reduced pressure. Crotonaldehyde and trifluoroacetic anhydride were fractionally distilled under N_2. Dimethyl sulfoxide and 1,2-dibromoethane were predried, then fractionally distilled under reduced pressure. All other reagents and solvents were reagent grade unless otherwise indicated. Ozone was generated using a Welsbach Ozonator. Analytical thin-layer chromatography was carried out by using E. Merck precoated silica gel 60F-254 plates and all flash chromatography used E. Merck silica gel 60 (230–400 mesh ASTM).

^1H NMR spectra were recorded on a Bruker WM-300 spectrometer at 300 MHz. ^{13}C NMR spectra were recorded on a JEOL JNM-FX90Q spectrometer at 22.49 MHz. Chemical shifts (δ) in $CDCl_3$ are expressed in ppm downfield from internal Me_4Si. IR spectra were recorded on a Perkin-Elmer Model 681 infrared spectrophotometer and are reported in reciprocal centimeters. Mass spectra were obtained on a computerized AEI MS-902 instrument using electron impact ionization at 70 eV (EI) or chemical ionization with isobutane reagent gas (CI). Specific optical rotations were measured on a Perkin-Elmer Model 141 polarimeter; concentrations (*c*) are expressed as g/100 cm^3 solvent ($CHCl_3$). Melting points were determined on a Thomas-Hoover Unimelt apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Preparation of 6 and 7. To a stirred solution of (2S),(3S)-geraniol 2,3-epoxide (3.56 g, 20.9 mmol)[12] in 2:3 ethanol:water (45 mL) at room temperature was added NaCN (14.0 g, 0.29 mol), and the resulting solution was heated at reflux for 5.5 h. The ethanol was removed in vacuo and the aqueous residue was extracted with ether (3 × 15 mL). The ether extracts were discarded. The aqueous phase was diluted with water (50 mL), then carefully acidified to pH 3–4 with concentrated H_2SO_4 at 0 °C. The acidification was performed in an efficient fume hood and the discharged HCN was passed through a 3 N NaOH solution (300 mL). The aqueous phase was then saturated with NaCl and extracted with ether (6 × 80 mL). The combined ether extracts were dried ($MgSO_4$) and concentrated to a mixture of acids (3.3 g) containing **5** as the major product. The crude acids were dissolved in benzene (50 mL), *p*-toluenesulfonic acid (2 mol%) was added, and the solution was heated at reflux with azeotropic removal of water for 1 h. The benzene was removed in vacuo and the remaining brown oil was flash chromatographed (55:45 hexane:ethyl acetate) to provide **6** as a colorless oil (1.54 g, 37%); $[\alpha]_D$ −4.4° (*c* 1.77, $CHCl_3$); ^1H NMR 5.05 (m, 1 H), 4.25 (dd, 1 H, *J* = 4.4, 7.0 Hz), 2.89 (dd, 1 H, *J* = 7.0, 18.0 Hz), 2.53 (dd, 1 H, *J* = 4.4, 18 Hz), 2.08 (m, 2 H) 1.66, 1.59, 1.39 (3 s, 9 H); ^{13}C NMR 175.9, 132.1, 122.7, 90.5, 71.7, 38.8, 37.7, 25.2, 22.0, 18.2, 17.2; IR (film) 3470, 2940, 1764; CIMS, *m/e* 199 (M + 1, 52%), 181 (M + 1 − H_2O, 100%).

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.13. Found: C, 66.50; H, 9.05.

This chromatography also afforded **7** as a less polar, colorless oil (0.15 g, 3.6%); $[\alpha]_D$ 10.8° (*c* 4.05, $CHCl_3$); ^1H NMR 5.05 (m, 1 H), 4.41 (dd, 1 H, *J* = 5.6, 9.8 Hz), 4.29 (dd, 1 H, *J* = 4.0, 5.6 Hz), 4.04 (dd, 1 H, *J* = 4.0, 9.8 Hz), 2.06 (m, 2 H), 1.65–1.45 (m, 2 H), 1.67, 1.59, 1.21 3 s, 9 H); ^{13}C NMR 181.2, 132.6, 122.9, 73.1, 72.0, 47.0, 35.7, 25.5, 22.6, 17.5, 15.0; IR (film) 3450, 2930, 1764; CIMS, *m/e* 199 (M + 1, 100%) 181 (M + 1 − H_2O, 3.5%).

Preparation of 9. Normal butyllithium (2.36 M in hexane, 3.85 mL, 9.09 mmol) was added to a stirred solution of isopropylcyclohexylamine (1.49 mL, 9.09 mmol) in dry THF (3.6 mL) under Ar at 0 °C. After 30 min the solution was cooled to −78 °C and a white suspension formed. A solution of **6** (0.60 g, 3.03 mmol) in dry THF (3.6 mL) was then added dropwise and the resulting homogeneous yellow solution was stirred at −78 °C for 25 min. A solution of CH_3I (0.94 mL, 15.2 mmol) and HMPA (1.2 mL) in dry THF (2.4 mL) was then added dropwise over a 5-min period. After stirring an additional 10 min, the reaction mixture was warmed to −35 °C for 1 h and then quenched with saturated aqueous NH_4Cl (2 mL) and water (6 mL). The THF was removed in vacuo and the aqueous phase was extracted with ether (6 × 10 mL). The combined ether extracts were dried ($MgSO_4$) and concentrated in vacuo, and the crude product was flash chromatographed (3:2 hexane:ethyl acetate) to provide **9** as a colorless oil (0.57 g, 89%); $[\alpha]_D$ 0.9° (*c* 2.15, $CHCl_3$); ^1H NMR 5.08 (m, 1 H), 3.82 (d, 1 H, *J* = 10.0 Hz), 2.63 (dq, 1 H, *J* = 7.1, 10.0 Hz), 2.10 (m, 2 H), 1.85–1.75 (m, 2 H), 1.68, 1.60, 1.32 (3 s, 9 H), 1.28 (d, 3 H, *J* = 7.1 Hz); ^{13}C NMR 175.4, 132.5, 123.6, 86.0, 80.4, 42.2, 40.2, 25.4, 22.4, 18.7, 17.6, 12.8; IR (film) 3435, 2930, 1760; CIMS, *m/e* 213 (M + 1, 100%), 195 (M + 1 − H_2O, 51%), 139 (12%).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.71; H, 9.60.

Preparation of 10. A Rubin Ozonizer[26] was used to deliver a saturated ozone solution (0.04 M, 1.63 mmol O_3 in 41 mL, CH_2Cl_2) at −78 °C to a stirred solution of lactone **9** (0.308 g, 1.45 mmol) in CH_2Cl_2 (20 mL) also at −78 °C. After 3 min, dimethylsulfide (0.65 mL, 8.4 mmol) was added and the reaction mixture was warmed to room temperature. The CH_2Cl_2 was concentrated in vacuo and the crude product was flash chromatographed (35:65 hexane:ethyl acetate) to provide **10** as a colorless oil (0.235 g, 85%); $[\alpha]_D$ 1.5° (*c* 2.03, $CHCl_3$); ^1H NMR 9.80 (d, 1 H, *J* = 0.8 Hz), 3.77 (d, 1 H, *J* = 10.2 Hz), 2.69–2.61 (m, 3 H), 2.06, 2.00 (AB, ddd, 2H, *J* = 7.4, 14.7, 22.1 Hz), 1.32 (s, 3 H), 1.28 (d, 3 H, *J* = 7.1 Hz); ^{13}C NMR 201.5, 176.3, 85.5, 79.2, 41.2, 38.0, 31.1, 18.5, 12.3; IR (film) 3425, 2941, 2725, 1764, 1724; CIMS, *m/e* 187 (M + 1, 100%), 169 (56%).

Preparation of 11. Carbon tetrabromide (97 g, 0.292 mol) was added to a stirred solution of triphenylphosphine (77 g, 0.292 mol) in CH_2Cl_2 (0.4 L) under Ar at 0 °C. After 10 min, zinc dust (19.1 g, 0.292 mol) was added, and the deep red suspension was stirred for 22 h at room temperature. Crotonaldehyde (10 mL, 0.146 mol) was carefully added at 0 °C and the reaction mixture was stirred at room temperature for 2 h and then poured into rapidly swirling ice-cooled pentane (2 L). The pentane solution was filtered and the remaining brown tarry residue was repeatedly washed with portions of ice-cold pentane (4 × 300 mL). The pentane fractions were combined and concentrated in vacuo. The crude product was flash chromatographed (pentane) to provide the unstable (*E*)-1,1-dibromo-*trans*-1,3-pentadiene (23 g, 70%) which was used immediately in the next reaction: ^1H NMR 6.87 (d, 1 H, *J* = 10.1 Hz), 10.1, 15.2 Hz), 5.90 (dq, 1 H, *J* = 6.6, 15.2 Hz), 1.75 (dd, 3 H, *J* = 1.3, 6.6 Hz); IR (film) 2900.

To a stirred solution of the dibromodiene (21.2 g, 93.8 mmol) in dry ether (35 mL) at −78 °C under Ar was added methyllithium in ether (1.5 M, 130 mL, 0.195 mol) over 7 min. The reaction

(22) (a) Chan, T. H.; Mychajlowskij, W. *Tetrahedron Lett.* **1974**, 3479. (b) Chan, T. H.; Law, P. W. K.; Li, M. P. *Ibid.* **1976**, 2667. (c) Hudrlik, P. F.; Hudrlik, A. M. Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809.

(23) (a) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329. (b) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, *165*.

(24) Diol **16**, prepared by catalytic hydrogenation of **15**, underwent simultaneous oxidation of both hydroxyl groups to afford (+)-tetrahydrovertinolide (ref 10) in 70% yield.

(25) For the oxidation of β-hydroxy esters cf.: Smith, A. B., III; Levenberg, P. *Synthesis* **1981**, 567.

mixture was slowly warmed to room temperature, and after 17 h Me_3SiCl (12.9 mL, 0.101 mol) was added dropwise. After an additional 2 h the reaction mixture was added to a rapidly stirred cold aqueous 2.5% HCl solution (140 mL). The layers were separated, and the aqueous layer was extracted with ether (50 mL). The combined ether layers were washed with water (2 × 50 mL) to neutral pH and then dried ($MgSO_4$). The ether was removed at atmospheric pressure and the residue was fractionally distilled to yield 1-(trimethylsilyl)-*trans*-3-penten-1-yne as a colorless liquid (8.9 g, 69%): bp 66–67.5 °C (40 mmHg), (lit.[27] bp 68 °C, 46 mmHg); ^1H NMR 6.20 (dq, 1 H, J = 6.8, 15.8 Hz), 5.49 (dq, 1 H, J = 1.9, 15.8 Hz), 1.75 (dd, 3 H, J = 1.9, 6.8 Hz), 0.16 (s, 9 H); IR (film) 2970, 2170, 2130, 1250, 1080, 845.

To a stirred solution of the silyl enyne (2.76 g, 20 mmol) in dry ether (13.5 mL) under Ar at room temperature was added diisobutylaluminum hydride in heptane (1 M, 21 mL, 21 mmol). After stirring at 40 °C for 6.5 h and at room temperature for 14 h, the reaction mixture was cooled to 0 °C and a solution of CNBr in dry ether (2.0 M, 10 mL, 20 mmol) was added. The reaction mixture was stirred at room temperature for 1.5 h and then poured into cold 6 N NaOH (110 mL). The phases were separated and the aqueous phase was extracted with ether (4 × 100 mL). The combined ether extracts were dried ($MgSO_4$) and concentrated, and the crude product was flash chromatographed (pentane) to provide the silyl bromo diene **11** as a colorless oil (3.4 g, 78%). Diene **11** was stored as a 0.25 M solution in THF at −20 °C with a crystal of BHT added as a stabilizer: ^1H NMR (acetone-d_6) 7.26 (d, 1 H, J = 11.4 Hz), 6.25 (ddq, 1 H, J = 1.6, 11.4, 14.4 Hz), 5.86 (dq, 1 H J = 6.9, 14.4 Hz), 1.73 (dd, 3 H, J = 1.6, 6.9 Hz), 0.28 (s, 9 H); IR (film) 2960, 1645, 1250; CIMS m/e 218, 220, (M + 1, 19%) 139 (100%).

Preparation of 14. A 1 M solution of anhydrous $MgBr_2$ in 3:1 ether:benzene[20] was prepared by addition of 1,2-dibromoethane (0.69 mL, 8 mmol) to a stirred suspension of magnesium turnings (0.2 g, 8.3 mmol) in 3:1 ether:benzene (8 mL) at a rate sufficient to maintain gentle reflux. Simultaneously, *sec*-BuLi (1.43 M in cyclohexane) was added dropwise to bromide **11** (1.1 g, 5 mmol) in dry THF (20 mL) at −78 °C under argon until TLC indicated the absence of **11**.

The 1 M $MgBr_2$ solution (6 mL, 6 mmol) was then added dropwise to **12** and the resulting suspension was stirred at −78 °C for 50 min to produce Grignard reagent **13**. A solution of aldehyde **10** (0.21 g, 1.11 mmol) in dry THF (5.5 mL) was rapidly added to **13** at −78 °C. The reaction mixture was stirred at −78 °C for 40 min, warmed to −60 °C for 30 min, and then quenched with saturated NH_4Cl. After warming to room temperature, the two-phase system was extracted with ethyl acetate (6 × 20 mL). The combined ethyl acetate extracts were dried ($MgSO_4$) and concentrated, and the crude product was flash chromatographed (8:7 hexane:ethyl acetate) to provide **14** as a mixture of diastereomers (0.24 g, 66%); ^1H NMR 6.73 (d, 1 H, J = 11.4 Hz), 6.32 (ddq, 1 H, J = 1.4, 11.4, 14.2 Hz), 5.75 (dq, 1 H, J = 6.9, 14.2 Hz), 4.26 (m, 1 H), 3.86 (dd, 1 H, J = 4.7, 10.1 Hz), 2.63 (dq, 1 H, J = 7.1, 10.1 Hz), 1.79 (dd, 3 H, J = 1.4, 6.9), 1.9–1.5 (m, 4 H), 1.32, 1.31 (2 s, 3 H), 1.28 (d, 3 H, J = 7.1 Hz), 0.19 (s, 9 H); IR (film) 3410, 2930, 1760, 1645, 1575; CIMS, m/e 327 (M + 1, 2%), 309 (24%), 291 38%), 173 (50%), 145 (54%), 107 (55%), 93 (100%).

Preparation of 15. To a stirred solution of **14** (0.21 g, 0.64 mmol) in dry THF (1.5 mL at room temperature under Ar was added a 1 M solution of $(n\text{-Bu})_4NF$ in THF (1.92 mmol, 1.92 mL). After 1 h the reaction mixture was heated to 45 °C. After 4 h the reaction mixture was quenched with water. The aqueous phase was saturated with NaCl and then extracted with ethyl acetate (6 × 5 mL). The combined ethyl acetate extracts were dried ($MgSO_4$) and concentrated, and the crude reaction product was flash chromatographed (45:55 hexane:ethyl acetate) to provide **15** as a mixture of diastereomers (0.12 g, 73%); ^1H NMR 6.15 (dd, 1 H, J = 10.3, 15.0 Hz), 6.00 (dd, 1 H, J = 10.3, 14.7 Hz) 5.71 (dq, 1 H, J = 6.8, 14.7 Hz), 5.52 (dd, 1 H, J = 7.2, 15.0 Hz), 4.13 (m, 1 H), 3.85 (dd, 1 H, J = 2.1, 10.1 Hz), 2.63 (dq, 1 H, J = 7.1, 10.1 Hz), 1.74 (d, 3 H, J = 6.8 Hz), 1.9–1.5 (m, 4 H), 1.32, 1.31 (2 s, 3 H), 1.28 (d, 3 H, J = 7.1 Hz); IR (film) 3420, 2940, 1760, 1665, 1575; CIMS, m/e 255 (M + 1, 0.4%), 237 (13%), 219 (11%), 145 (13%), 135 (12%), 107 (55%), 93 (100%).

Preparation of 17. Manganese dioxide (Aldrich, 0.27 g, 3.1 mmol) was added to a stirred solution of **15** (79 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) at room temperature. After 1.5 h the reaction mixture was filtered through Celite and the solid residue was repeatedly washed with 1:9 methanol:CH_2Cl_2 (3 × 4 mL). The combined organic layers were concentrated in vacuo and the crude product flash chromographed (55:45 hexane:ethyl acetate) to afford **17** as a colorless oil (57 mg, 73%); $[\alpha]_D$ −17.5° (c 4.10, $CHCl_3$); ^1H NMR 7.17 (dd, 1 H, J = 9.7, 15.6 Hz), 6.26–6.17 (m, 2 H), 6.07 (d, 1 H, 15.6 Hz), 3.71 (d, 1 H, J = 10.4 Hz), 2.80–2.60 (m, 3 H) 2.05 (m, 2 H), 1.87 (d, 3 H, J = 5.2 Hz), 1.33 (s, 3 H), 1.27 (d, 3 H, J = 7.1 Hz); ^{13}C NMR 200.6, 176.0, 144.2, 141.5, 130.0, 126.9, 85.7, 79.4, 75.5, 41.1, 39.3, 33.0, 18.9, 18.8, 12.6; IR (film) 3450, 2940, 1776, 1686, 1661, 1640, 1597; CIMS, m/e 253 (M + 1, 100%), 235 (23%).

(*S*)-(−)-Vertinolide. To a stirred solution of Me_2SO (45 μL, 0.62 mmol) in dry CH_2Cl_2 (1 mL) at −78°C under Ar was added trifluoroacetic anhydride (51 μL, 0.35 mmol). The resulting white slurry was stirred for 30 min, then a −78 °C solution of **17** (45 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) was added. The resulting homogeneous solution was stirred for 15 min at −78 °C. Triethylamine (99 μL, 0.71 mmol) was added and the reaction mixture was stirred at −78 °C for 11 min. Water (2 mL) was added and reaction mixture allowed to warm to room temperature. The aqueous phase was saturated with NaCl and extracted with ethyl acetate (6 × 3 mL). The combined ethyl acetate phase was dried ($MgSO_4$) and concentrated. The crude product was taken up in ether (1.5 mL) and washed with saturated aqueous $NaHCO_3$ (2 mL). The ether phase was discarded and the aqueous layer acidified to pH 2 using 10% aqueous HCl saturated with NaCl. After extracting with ethyl acetate (6 × 3 mL), the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The product was then flash chromatographed (94:6 $CHCl_3$:ethanol) to provide synthetic (*S*)-(−)-vertinolide (35 mg, 80%, which was spectroscopically and chromatographically identical with an authentic sample of the natural product. The synthetic sample was further purified by recrystallization from ethyl acetate–ether: $[\alpha]_D$ −22° (c 0.054, $CHCl_3$); mp 146–149 °C dec [lit.[10] $[\alpha]_D$ −25° (c 0.05, $CHCl_3$), mp 149.2–152.3 °C dec]; ^1H NMR 7.17 (dd, 1 H, J = 10.1, 15.5 Hz), 6.35–6.10 (m, 2 H), 6.03 (d, 1 H, J = 15.5 Hz), 2.75–2.40 (m, 2 H), 2.25 = 2.05 (m, 2 H), 1.87 (d, 3 H, J = 6.0 Hz), 1.68 (s, 3 H), 1.49 (s, 3 H); ^{13}C NMR (acetone-d_6) 189.9, 176.2, 173.5, 143.3, 140.6, 131.2, 128.4, 97.0, 83.2, 34.7, 31.5, 23.5, 18.7, 6.3; IR ($CHCl_3$) 3600–2400, 2940, 1745, 1690, 1675, 1640, 1595; EIMS, m/e 250 (M^+, 2.7%), 235 (3.8%), 151 (1.9%), 108 (29%), 99 (14.1%), 95 (100%), 67 (23.2%), 41 (14.0%); CIMS, m/e 251 (M + 1, 24%), 183 (15%), 108 (43%), 95 (100%), 67 (23%).

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