Supporting Information

Synthesis of 4-Methyldienoates Using a Vinylogous Horner-Wadsworth-Emmons Reagent. Application to the Synthesis of Trichostatic Acid

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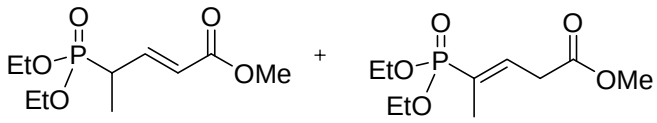
Contents:

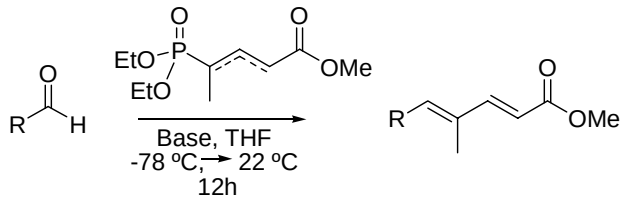
General Methods: All reactions were performed under an inert atmosphere unless otherwise noted. All spectra were recorded in $CDCl_3$, and chemical shifts are given relative to $CHCl_3$ (7.27 ppm for ^1H NMR) or $CDCl_3$ (77.23 ppm for ^{13}C NMR). The following abbreviations designate multiplates: bs (broad singlet), bt (broad triplet).



Methyl (*E*)-4-(diethoxyphosphoryl)-2-pentenoate and methyl (*Z*)-4-(diethoxyphosphoryl)-3-pentenoate (1). A soln of (*E*)-methyl 4-brom-2-pentenoate (4.02 g, 20.8 mmol, 1.03 equiv) and triethyl phosphite (3.36 g, 2.02 mmol, 1 equiv) was heated to 160 ºC for 18 h and cooled to 22 ºC. The crude reaction mixture was chromatographed (silica, 0-100% EtOAc in hexanes) to afford starting material (1.28 g) and **1** (1.77 g, 50% based upon recovered starting material) [1] as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ (both isomers) 7.02-6.88 (m, 0.5H), 6.66 (dt, J = 23.1, 14.1 Hz, 1H), 5.91 (ddd, J = 18.6, 4.8, 1.4 Hz, 1H), 4.15-3.99 (m, 4H), 3.70 (s, 1.5H), 3.67 (s, 3H), 3.20 (m, 2H), 2.80 (m, 1H), 1.81 (d, J = 14.4 Hz, 3H), 1.39-1.26 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (both isomers) 13.2 (d, $J_{H\text{-}P}$ = 5.25 Hz) , 16.5 (d, $J_{H\text{-}P}$ = 6.12 Hz), 16.6 (d, $J_{H\text{-}P}$ = 5.75 Hz), 34.2, 34.3 (d, $J_{H\text{-}P}$ = 163.3 Hz), 36.5, 51.9 (d, $J_{H\text{-}P}$ = 2.3 Hz), 52.4, 62.0 (d, $J_{H\text{-}P}$ = 5.25 Hz), 62.6 (d, $J_{H\text{-}P}$ = 7.0 Hz), 123.0 (d, $J_{H\text{-}P}$ = 12.75 Hz), 128.7 (d, $J_{H\text{-}P}$ = 178.8 Hz), 136.8(d, $J_{H\text{-}P}$ = 13.5 Hz), 144.9 (d, $J_{H\text{-}P}$ = 9.4 Hz), 166.6, 170.8; ^{31}P NMR (300 MHz, $CDCl_3$); δ (both isomers) 27.2, 20.0; IR (neat) 2984, 1739, 1648, 1438, 1250,

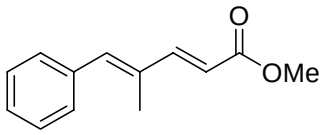
[1] We found heating for an extended amount of time was necessary to push the reaction towards completion during which time the product had decomposed substantially

1052, 1023, 965, 791 cm^{-1}; HRMS (FAB) for $C_{10}H_{19}O_5P$ $[M+H]^+$ calcd 251.1048, found 251.1045.

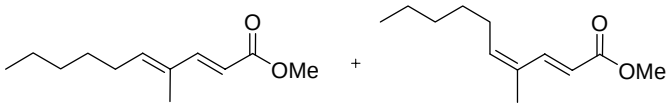


Synthesis of 4-Methyldienoates Using Phosphonate 1. General Procedure A soln of phosphonate **1** (110 mg, 0.44 mmol, 1.5 equiv) in anhyd solvent was cooled to -78 ºC, and a commercial soln of the amide base (0.4 mmol, 1.4 equiv)[2] was added dropwise. The soln was warmed to 22 ºC for 30 min and recooled to -78 ºC. A soln of the aldehyde (0.3 mmol, 1 equiv) was added dropwise. The soln was stirred for 12 h, and the temperature was allowed to rise to 22 ºC. After the formation of product had ceased (TLC monitoring), the reaction was quenched by the addition pH 7 phosphate buffer (1M, 1 mL). The soln was combined with CH_2Cl_2 (15 mL) and NaCl sat. aq. soln (10 mL), extracted with CH_2Cl_2, dried with $MgSO_4$, and the solvent was removed under reduced pressure to afford the crude compound along with a small amount of unreacted phosphonate. A known quantity of mesitylene was added. NMR yields were measured using ^1H NMR integration of the olefinic and mesitylene signals. Extended relaxation times were required in order to obtain accurate results. The products were purified by column chromatography (silica). In some cases the *E*,*E*-product could be separated from the mixture.

[2] The commercial soln was titrated prior to use following a literature procedure: Ireland, R. E.; Meissner, R. S. *J. Org. Chem.* **1991**, *56*, 4566.



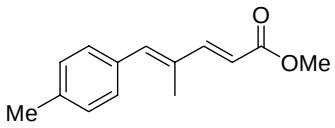
Methyl (2*E*,4*E*)-4-methyl-5-phenylpenta-2,4-dienoate (2a).[3] Following the general procedure above, **2a** (160 mg, 82%) was isolated after flash column chromatography as a pure *E*,*E*-isomer (0→100% CH_2Cl_2/hexanes; silica) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 16, 0.8 Hz, 1H), 7.42-7.27 (m, 5 H), 6.87 (bs, 1H), 5.99 (d, *J* = 16 Hz, 1H), 3.80 (s, 3H), 2.06 (d, *J* = 1.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) 167.9, 150.2, 139.2, 136.8, 134.2, 129.6, 128.5, 127.9, 117.2, 51.7, 13.9; IR (neat) 2950 (w), 1718 (s), 1656 (w), 1613 (m); HRMS (ESI) calcd for $C_{13}H_{14}O_2Na$ $[M+Na]^+$ calcd 225.0886, found 225.0878.



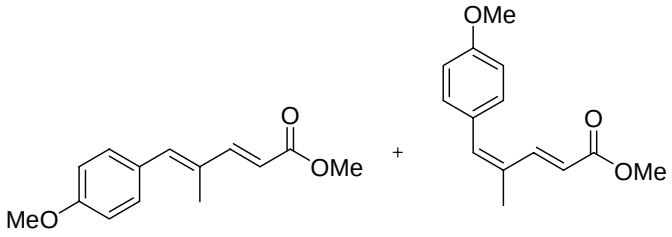
Methyl (2*E*,4*E*)-4-methyldeca-2,4-dienoate (2b). Following the general procedure above, **2b** (139 mg, 97%) was isolated after flash column chromatography(0-10% EtOAc/hexanes) as a 1:1 mixture of *E*,*E*- and *E*,*Z*-isomers (partial separation occurred during purification) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 16.0, 0.8 Hz, 1 H), 7.33 (dd, *J* = 16.0, 0.8 Hz, 1H), 2.27 (dd, *J* = 7.4, 7.4 Hz, 2H), 2.20 (dd, *J* = 7.4, 7.4 Hz, 2H), 1.86-1.85 (m, 3H), 1.78-1.77 (m, 3H), 1.48-1.26 (m, 12H, CH_2), 0.90 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) 168.3 167.9, 150.2, 149.9, 142.9, 142.7, 132.9, 132.8, 115.6, 115.1, 60.4, 51.7, 31.7, 31.6, 29.0, 28.9, 22.7, 14.6, 14.2, 12.4, 12.3; IR

[3] (a) Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 15028. (b) Mitsudo, T.-a.; Zhang, S.-W.; Nagao, M.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 598. (c) Eberbach, W.; Burchardt, B. *Chem. Ber.* **1978**, *111*, 3665.

(neat) 2953 (s), 1725 (s), 1659 (m); HRMS (ESI) calcd for $C_{24}H_{41}O_4$ $[2M+H]^+$ 393.2999, found 393.2986.



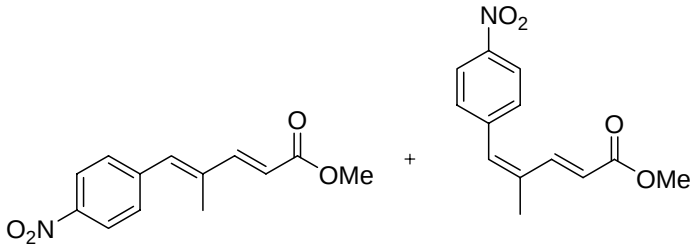
Methyl (2*E*,4*E*)-4-methyl-5-(*p*-tolyl)penta-2,4-dienoate (2c). Following the general procedure above, **2c** (56 mg, 78%) was isolated after flash column chromatography as a pure *E*,*E*-isomer (0→15% CH_2Cl_2/hexanes; silica) as a colorless amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd *J* = 16, 0.8 Hz, 1H), 7.27 (d, *J* = 8 Hz, 2H), 7.20 (d, *J* = 8 Hz, 2H), 6.83 (bs, 1H), 5.97 (d, *J* = 16 Hz, 1H), 3.79 (s, 3H), 2.38 (s, 3H), 2.06 (d, *J* = 0.8 Hz, 3H); (lit[4] ^{1}H NMR); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.1, 154.5, 139.4, 138.0, 134.0, 133.5, 129.7, 129.3, 116.8, 51.7, 21.5, 13.9.



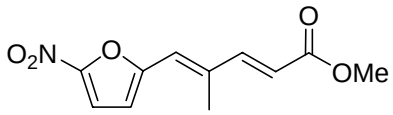
Methyl (2*E*,4*E*)- and (2*E*,4*Z*)-5-(4-methoxyphenyl)-4-methylpenta-2,4-dienoate (2d). Following the general procedure above, **2d** (41 mg, 59%) was isolated after column chromatography (12% EtOAc/hexanes; silica) as a 94:6 mixture of *E*,*E*- and *E*,*Z*-isomers as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 16.0, 0.8 Hz, 1H), 7.51 (dd, *J* = 16.0, 0.8 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.2 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.80 (s, 1H), 6.76 (s, 1H), 6.01 (dd, *J* = 16.0, 0.8 Hz, 1H) 5.95 (d, *J* = 16.0

[4] Rebuffat, S.; Davoust, D.; Giraud, M.; Molho, D. *Bull. Soc. chim. Fr. Part 2. Chim. Molec. Org. Biol.* **1974**, 2892.

Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.06 (d, J = 1.2 Hz, 3H), 2.03 (d, J = 1.2 Hz, 3H); (lit[4,5] ^{1}H NMR); ^{13}C NMR (150 MHz, $CDCl_3$, *E,E* only) δ 168.1, 159.4, 150.7, 139.1, 132.6, 131.2, 129.5, 116.3, 114.0, 55.5, 51.7, 13.9.



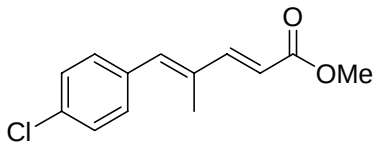
Methyl (2*E*,4*E*)- and (2*E*,4*Z*)-4-methyl-5-(4-nitrophenyl)penta-2,4-dienoate (2e). Following the general procedure above, **2e** (73 mg, 82%) was isolated after chromatography (0→50% EtOAc/hexanes; silica) as an 86:14 mixture of *E*,*E* and *E*,*Z* isomers (isomerization occurred during purification) as a pale yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.8 Hz, 2H), 7.67 (dd, J = 16.0, 0.8 Hz, 1H), 7.52-7.48 (m, 3H), 7.40 (d, J = 8.4 Hz, 2H), 6.88 (bs, 1H), 6.82 (bs, 1H), 6.13 (d, J = 16.0 Hz, 1H), 6.09 (d, J = 16.0 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 2.11 (d, J = 1.6 Hz, 3H), 2.08 (d, J = 1.2 Hz, 3H); (lit[6] ^{1}H NMR).



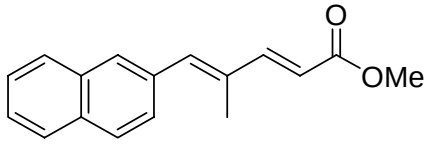
Methyl (2*E*,4*E*)-4-methyl-5-(5-nitrofuran-2-yl)penta-2,4-dienoate (2f). Following the general procedure above, **2f** (58 mg, 87%) was isolated after flash column chromatography (20-40% EtOAC/hexanes; silica) as a pure *E*,*E*-isomer as a yellow-green

[5] Naskar, D.; Roy, S. *Tetrahedron*, **2000**, *56*, 1369.
[6] Koyama, Y.; Kyomura, N.; Oishi, J.-I.; Yamagishi, S. *Yakugaku Zasshi*, **1975**, *95*, 1210.

crystalline solid: mp 165-166 ºC; (lit[7] mp = 166-167 ºC); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 15.0, 1.2 Hz, 1H), 7.38 (d, *J* = 4.2 Hz, 1H), 6.65 (d *J* = 4.2 Hz, 1H), 6.56 (bs, 1H), 6.16 (d, *J* = 15.0 Hz 1H), 3.81 (s, 3H), 2.28 (d, *J* = 0.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 154.7, 147.7, 139.4, 122.8, 120.8, 114.8, 113.6, 52.0, 14.5.



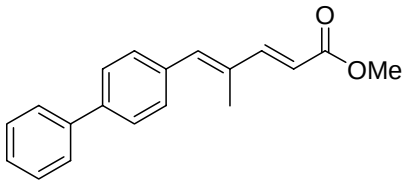
Methyl (2*E*,4*E*)-5-(4-chlorophenyl)-4-methylpenta-2,4-dienoate (2g). Following the general procedure above, **2g** (65 mg, 93 %) was isolated after flash column chromatography (0→10% EtOAc/hexanes; silica) as a pure *E*,*E*-isomer as a colorless crystalline solid: mp = 76-77 ºC ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 16.0, 0.8 Hz, 1 H), 7.36 (dd *J* = 6.4, 2 Hz, 2H), 7.28 (dd, *J* = 6.8, 2.0 Hz, 1H), 6.80 (bs 1H), 6.00 (dd, *J* = 15.0, 0.8 Hz, 1H), 3.80 (s, 3 H, OCH_3) 2.03 (d, *J* = 1.2 Hz, 3H); (lit[4] ^{1}H NMR) ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.9, 149.8, 137.7, 135.3, 134.8, 133.8, 130.9, 128.8, 117.7, 51.8, 13.9.



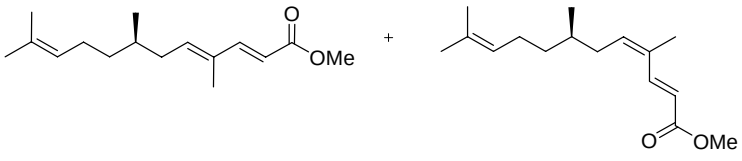
Methyl (2*E*,4*E*)-4-methyl-5-(naphthalen-3-yl)penta-2,4-dienoate (2h). Following the general procedure above, **2h** (69 mg, 91%) was isolated after flash column chromatography (0-15% EtOAc/hexanes; silica) as a pure *E*,*E*-isomer as a colorless solid:

[7] Ogawa, H; Saikachi, H. *Synthesis*, **1972**, 138.

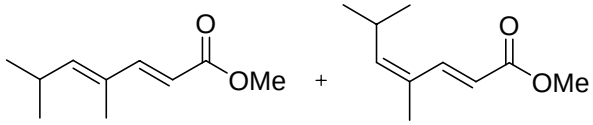
mp 58-59 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.82 (m, 4 H, ArH), 7.58 (dd, *J* = 16.0, 0.8 Hz, 1H), 7.52-7.47 (m, 3H), 7.02 (bs, 1H), 6.04 (d, *J* = 16.0 Hz, 1H), 3.81 (s, 3H), 2.15 (d, *J* = 1.2, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) 167.8, 150.0, 139.1, 134.4 134.1, 133.1, 132.6, 128.8, 128.2, 127.9, 127.6, 127.2, 126.5, 126.4, 117.1, 51.6, 13.9; IR (film) 2946 (w), 1718 (s), 1613 (s); HRMS (ESI) calcd for $C_{17}H_{16}O_2Na$ $[M+Na]^+$ 275.1043, found 275.1027.



Methyl (2*E*,4*E*)-5-[1,1'-biphenyl]-4-methylpenta-2,4-dienoate (2i). Following the general procedure above, **2i** (72 mg, 87%) was isolated after flash column chromatography (0-70% CH_2Cl_2/hexanes; silica) as a pure *E*,*E*-isomer as a colorless crystalline solid: mp 102-104.5 ºC; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64-7.62 (m, 4H), 7.54 (dd, *J* = 16.0, 0.6 Hz, 1H), 7.48-7.44 (m, 4H), 7.39-7.36 (m, 1H), 6.90 (bs, 1H), 6.60 (d, *J* = 16.0 Hz, 1H) 3.81 (s, 3H), 2.12 (d, *J* = 0.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) 168.0, 150.3, 140.7, 140.6, 138.8, 135.8, 134.4, 130.2, 129.1, 127.7, 127.3, 127.2, 117.2, 51.8, 14.1; IR (KBr) 3031 (w) 2950 (w), 1710 (s), 1612 (w); HRMS (ESI) calcd for $C_{19}H_{18}O_2Na$ $[M+Na]^+$ 301.1199, found 301.1186.

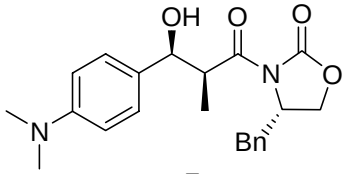


Methyl (7*R*,2*E*,4*E*)- and (7*R*,2*E*,4*Z*)-4,7,11-trimethyldodeca-2,4,10-trienoate (2j). Following the general procedure above, **2j** (61 mg, 78%) was isolated after flash column chromatography (0→2% EtOAc/hexanes; silica) as a 77:23 mixture of *E*,*E*- and *E*,*Z*-isomers as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 16.0, 0.6 Hz, 1H), 7.34 (dd, *J* = 16.0, 0.6 Hz, 1H), 5.94-5.90 (m, 1H,), 5.88 (d, *J* = 16.0 Hz, 1H,), 5.78 (d, *J* = 16.0 Hz, 1H), 5.71-5.70 (m, 1H) 5.10-5.06 (m, 1H), 3.76 (s, 1H), 3.75 (s, 3H), 2.30-1.92 (m, 4H), 1.85-1.87 (m, 3H), 1.78-1.76 (m, 3H), 1.69-1.67 (m, 3H), 1.62-1.53 (m, 1H), 1.60-1.58 (m, 3H), 1.39-1.31 (m, 1H), 1.22-1.15 (m, 1H), 0.90-0.88 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.3, 168.2, 150.2, 141.6, 139.1, 133.5, 131.5, 131.4, 124.8, 124.7, 117.7, 115.1 51.7, 51.6, 37.0, 36.9, 36.2, 35.3, 33.3, 33.2, 25.9, 25.8, 20.3, 19.8, 19.7, 17.8, 12.4; IR (neat) 2929 (s), 1725 (s), 1665 (m); HMRS (ESI) calcd for $C_{16}H_{26}O_2Na$ $[M+Na]^+$ 273.1825, found 273.1814.



Methyl (2*E*,4*E*)- and (2*E*,4*Z*)- 4,6-dimethylhepta-2,4-dienoate and (2k). Following the general procedure above, **2k** (44 mg, 80%) was isolated after flash column chromatography (0-10% EtOAc/hexanes; silica) as a 60:40 mixture of *E*,*E*- and *E*,*Z*-isomers (partial isomer separation occured during purification) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$), 7.78 (d, *J* = 16, Hz, 1H), 7.31 (dd, *J* = 16, 0.4 Hz, 1H), 5.87 (dd, *J* = 16, 0.8 Hz, 1H), 5.80 (dd, *J* = 16, 0.8 Hz, 1H), 5.72 (bd, *J* = 9.2 Hz, 1H), 5.56 (bd, *J* = 10 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.0-2.8 (m, 1H), 2.5-2.3 (m, 1H), 1.83 (d, *J* = 1.2 Hz, 3H), 1.78 (d, *J* = 1.2 Hz, 3H), 1.01 (d, *J* =6.4 Hz, 6H), 1.00 (d, *J* = 1.2 Hz,

6H); ^{13}C NMR (150 MHz, $CDCl_3$), 168.3, 168.2, 150.4 149.7, 147.4, 141.7, 130.7, 128.5, 117.8, 115.4, 51.7, 51.6, 28.1, 27.3, 23.3, 22.6, 20.2, 12.3; IR (neat) 2958 (m), 1725 (m), 1644 (s); HMRS (ESI) calcd for $C_{10}H_{16}O_2Na$ $[M+Na]^+$ 191.1043, found 191.1040.

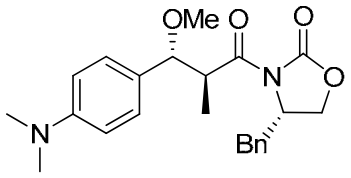


7

(4*S*)-4-Benzyl-3-[(2*S*,3*S*)-3-[4-(dimethylamino)phenyl]-3-hydroxy-2-methylpropanoyl]-1,3-oxalan-2-one (7)[8]: A soln of di-*n*-butylboryl trifluoromethanesulfonate (52 mmol, 52 mL, 1 M) was added dropwise to a soln of (*S*)-3-(1-oxoprop-1-yl)-4-(phenylmethyl)-1,3-oxazolidin-2-one (42 mmol, 9.8 g) in CH_2Cl_2 (300 mL) cooled to 0 ºC, such that the temperature did not rise above 4 ºC. The resulting soln turned tan in color. Et_3N (55 mmol, 5.5 g, 7.6 mL) was added slowly, such that the reaction temperature did not rise above 4 ºC. The soln turned yellow in color. The reaction mixture was then cooled to -78 ºC. 4-Dimethyl-aminobenzaldehyde (46 mmol, 6.9 g) was added to the reaction mixture as a soln in methylene chloride (100 mL), such that the temperature did not rise above -70 ºC. The reaction was stirred at -78 ºC for 20 min, was warmed to 0 ºC, and stirred for 1 h at this temperature. The reaction was then cooled to -10 ºC and was quenched with a phosphate buffer (pH = 7.0, 55 mL), followed by methanol (100 mL), all while keeping the temperature under 10 ºC. A soln of 2:1 MeOH/30% H_2O_2 (aq) (150 mL) was added, such that the internal temperature did not rise above 10 ºC. The reaction stirred for 2 h at 0 ºC. Solvent was then removed *in vacuo*. The resulting residue was extracted with methylene chloride. The organic

[8] modified from a literature procedure: Gage, J. R.; Evans, D. A.; DeRussy, D. T.; Paquette, L. A. *Org. Synth.* **1990**, *68*, 83.

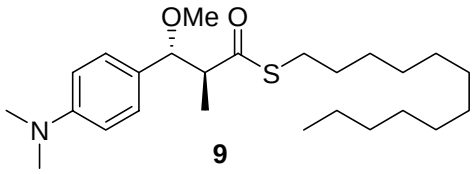
portions were combined and dried over $MgSO_4$. Solvent was removed *in vacuo* to give the crude product which was further purified by column chromatography (4:1 hexanes/EtOAc; silica, $R_f = 0.2$) to give **7** (15.8 g, 98%) as an pale yellow solid. Higher purity could be obtained by recrystallization from CH_2Cl_2/pentane, at the expense of yield: mp = 131-132 ºC dec; $[\alpha]_D^{20}$ = +76.4º (*c* = 0.97, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.16 (m, 7H), 6.69 (d, *J* = 9.0 Hz, 2H), 4.95 (dd, *J* = 5.1, 3.0 Hz, 1H), 4.51 (m, 1H), 4.17-4.06 (m, 2H), 3.98 (dd, *J* = 9.6, 7.5 Hz, 1H), 3.23 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.92 (s, 6H), 2.75 (dd, *J* = 13.5, 9.6 Hz, 1H), 2.70 (d, *J* = 3 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.77, 153.24, 150.36, 135.45, 129.72, 129.65, 127.64, 127.57, 127.31, 112.61, 74.55, 66.34, 55.61, 44.99, 40.96, 38.04, 12.02; IR (film) 3514, 2919, 1779, 1695, 1523, 1384, 1351, 1209, 816, 704 cm^{-1}; HMRS (FAB) calcd for $C_{22}H_{26}N_2O_4$ $[M]^{+\bullet}$ 382.1887, found 382.1884.



8

(4*S*)-4-Benzyl-3-[(2*S*,3*R*)-3-[4-(dimethylamino)phenyl]-3-methoxy-2-methylpropanoyl]-1,3-oxazolan-2-one (8): Oxazolidinone **7** (22 mmol, 8.3 g) was added to a 5-L round-bottom flask equipped with a stir bar. To this was added dry methanol (800 mL). Trifluoroacetic acid (45 mmol, 3.5 mL) was added until the pH dropped to 2-3. The reaction mixture was stirred for 16 h. Water was added until a colorless precipitate formed. The soln was allowed to sit for 5 h, then the precipitate was collected by vacuum filtration to give **8** (7.13 g, 81%) as a 3.1:1 mixture of diastereomers. These diastereomers were separated via flash chromatography (5:4.5:0.5,

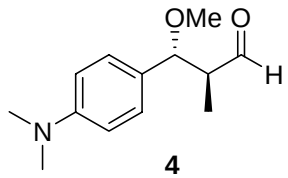
methylene chloride/hexanes/EtOAc; silica). Future separations could be effected by crystallization in CH_2CL_2/hexanes using a seed crystal obtained from the previous separation. The major isomer is characterized below: mp = 136.5-137 ºC; $[\alpha]_D^{20}$ = +138º (*c* = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.14 (m, 7H), 6.73 (d, *J* = 8.7 Hz, 2H), 4.82-4.72 (m, 1H), 4.30-4.15 (m, 4H), 3.31 (d, *J* = 13.0, 3.0 Hz, 1H), 3.10 (s, 3 H), 2.98 (s, 6H), 2.81 (dd, *J* = 13.5, 9.5 Hz, 1H), 0.94 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 153.5, 150.7, 135.7, 129.7, 129.1, 129.1, 127.5, 126.4, 112.4, 86.0, 66.2, 56.6, 55.7, 44.2, 40.7, 38.2, 14.8; IR (film) 2980, 2933, 2881, 1781, 1698, 1614, 1523, 1384, 1350, 1210, 1096, 819, 704 cm^{-1}; HRMS (FAB) for $C_{23}H_{28}N_2O_4$ $[M]^{+\bullet}$ calcd 396.2044, found 396.2044.



9

(2*S*,3*R*)-*S*-dodecyl 3-(4-(dimethylamino)phenyl)-3-methoxy-2-methylpropanethioate (9): To a round-bottom flask containing dodecanethiol (2.70 mL, 11.3 mmol) and a stir bar was added dry THF (50 mL). The reaction vessel was then stirred and cooled to 0 °C. Upon reaching this temperature, *n*-butyllithium (1.6 M in hexanes, 5.91 mL) was added dropwise, such that soln became white and cloudy. The reaction was allowed to warm to 25 °C and stir for 30 min. The reaction was then cooled to -78 °C before imide **8** (1.5 g, 3.78 mmol) was added dropwise as a soln in dry THF (10 mL). This mixture was allowed to stir at -78 °C for 10 min before warming to 25 °C. The reaction was monitored by TLC for consumption of starting material. After ~ 1 h, the reaction was quenched with satd ammonium chloride (aq) (20 mL). Satd sodium bicarbonate (aq) (50

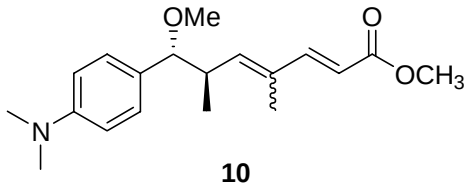
mL) was added, and the reaction mixture was extracted with methylene chloride (3 × 20 mL). The organic phases were combined and dried over sodium sulfate. Solvent was removed *in vacuo* to provide the crude product. The crude material was purified via flash chromatography (100% hexanes → 20% EtOAc/hexanes; silica) to give **9** (1.58 g, 99%) as a pale yellow oil: $[\alpha]_D^{20}$ = +72.0º (*c* = 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 9.0 Hz, 2H), 4.22 (d, *J* = 9.9 Hz, 1H), 3.11 (s, 3H), 2.97 (s, 6H), 2.93 (m, 3H), 1.61 (m, 2H), 1.27- 1.41 (m, 18H), 0.89 (t, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 4.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 150.7, 128.7, 126.6, 112.4, 85.8, 56.7, 55.5, 40.7, 32.1, 29.9, 29.8, 29.8, 29.7, 29.6, 29.4, 29.0, 22.9, 15.6, 14.3; IR (neat) 2925, 2854, 2818, 1690, 1614, 1523, 1455, 1351, 1096, 974, 946, 816 cm^{-1}; HRMS for $C_{25}H_{42}NSO_2$ $[M-H]^-$ calcd 420.2931, found 420.2931.



4

(2*S*,3*R*)-3-[4-(dimethylamino)phenyl]-3-methoxy-2-methylpropanal (4): 10% Pd/C (227 mg) was added to a round-bottom flask equipped with a stir bar and a rubber septum. Thioester **9** (1.58 g, 3.74 mmol) was added as a soln in dry acetone (5 mL). The reaction was allowed to stir under argon as triethylsilane (1.80 mL, 11.2 mmol) was added via syringe. After a short induction period (~3 min) gas was released vigorously. The reaction was allowed to stir for an additional 3 h. When TLC had confirmed that the reaction had gone to completion, the suspension was filtered through a plug of Celite, which was rinsed with acetone (5 mL). The solvent from the filtrate was removed *in vacuo*, leaving a residue that was further purified via flash chromatography (5%

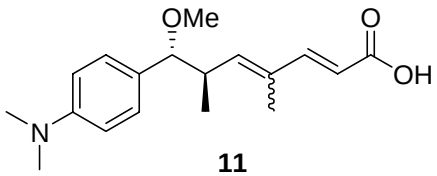
EtOAc/hexanes, silica) to provide **4** (658 mg, 79%): $[\alpha]_D^{20}$ = +63.4º (*c* = 0.76, $CHCl_3$) measured for a 94:6 mixture of **4** and its 2*R*,3*R* isomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (d, *J* = 3.0 Hz, 1H), 9.0 Hz, 2 H), 7.17 (d, *J* = 9.0 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 4.18 (d, *J* = 9.4 Hz, 1H), 3.16 (s, 3H), 2.98 (s, 6H), 2.81-2.60 (m, 1H), 0.84 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 128.7, 126.2, 112.4, 84.9, 56.5, 53.6 (impurity), 53.0 , 40.7, 11.2; IR (neat) 2932, 2820, 1727, 1614, 1523, 1351, 1084 cm^{-1}; HRMS (FAB) for $C_{13}H_{20}NO_2$ $[M+H]^+$ calcd 222.1494, found 222.1475. Epimerization has been detected in some cases with **4**. Epimerization was minimized by removal of solvents after column purification while cooling the solution to 0 ºC. The compound was redissolved in THF and used in the subsequent HWE reaction immediately after preparation. We suspect that some epimerization may have occurred under the basic conditions of the subsequent HWE reaction to account for the 87 % ee seen for trichostatic acid (**3**) at the end of the synthetic pathway. Another indication of the sensitivity of **4** is that when this compound is concentrated, it undergoes an elimination at room temperature with a half life of a couple days to produce a yellow solid.



10

Methyl (2*E*,4*E*,6*R*,7*R*)- and (2*E*,4*Z*,6*R*,7*R*)-7-[4-(dimethylamino)phenyl]-7-methoxy-4,6-dimethyl-2,4-heptadienoate (10): Phosphonate **1** (366 mg, 1.5 mmol) was dissolved in dry THF (10 mL). A soln of LiHMDS in THF (1.5 mL, 1.5 mmol, 1.0 M) was added slowly at -78 ºC. The soln was stirred for 30 min at -78 ºC, warmed to -40 ºC over 30 min, and then cooled back down to -78 ºC. Aldehyde **4** (259 mg, 1.2 mmol) was added

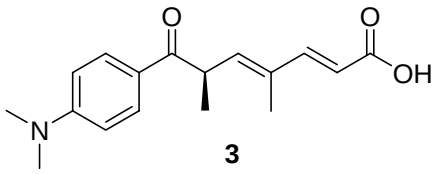
as a soln in THF (10 mL). The reaction mixture was allowed to slowly warm to 25 °C over 18 h. The reaction mixture was cooled to 0 ºC, and satd NH_4Cl (aq) was added. This mixture was stirred for an additional 30 min. The mixture was then extracted with diethyl ether. The organic phases were combined and dried over Na_2SO_4. Solvent was removed *in vacuo* to provide crude product. The product was purified by two consecutive chromatography columns (1st- 10% EtOAc/hexanes; silica, 2nd- 50% methylene chloride/47.5% hexanes/2.5% EtOAc; silica) to give **10** (271 mg, 71%) of the desired product as a ~2:1 mixture of *E*,*E* and *E*,*Z* isomers. : ^{1}H NMR ($CDCl_3$) δ 7.66 (d, *J* = 15.5 Hz, 1H), 7.37 (dd, *J* = 15.5, 0.5 Hz, 1H), 7.12 (m, 4H), 6.71 (d, *J* = 9.0 Hz, 4H), 5.87 (d, *J* = 9.5 Hz, 1H),5.84 (d, *J* = 15.5 Hz, 1H), 5.78 (d, *J* = 15.5 Hz, 1H), 5.70 (d, *J* = 9.0 Hz, 1H), 3.88 (d, *J* = 7.0 Hz, 1H), 3.86 (d, *J* = 7.5 Hz, 1H), 3.76 (s, 6 H), 3.15 (s, 6H), 3.06 (m, 1 H), 2.96 (m, 12H), 2.85 (m, 1H), 1.87 (d, *J* = 1.5 Hz, 3H), 1.71 (d, *J* = 1.0 Hz, 3H),0.85 (d, *J* = 7.0 Hz, 3H),0.85 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 168.2, 150.5, 150.4, 145.8, 145.7, 143.2, 143.2, 141.8, 132.7, 130.6, 128.6, 128.5, 128.4, 127.9, 127.8, 117.8, 115.2, 112.3, 88.2, 88.1, 56.9, 51.6, 40.8, 40.6, 39.6, 20.4, 18.1, 18.1, 17.1, 17.0, 12.6; IR (neat) 2928, 2818, 1719, 1615, 1522, 1435, 1350, 1276, 1169, 1103, 819 cm^{-1}; HRMS (FAB) for $C_{19}H_{28}NO_3$ $[M+H]^+$ calcd 318.2069, found 318.2044.



11

(2*E*,4*E*,6*R*,7*R*)- and (2*E*,4*Z*,6*R*,7*R*)-7-[4-(dimethylamino)phenyl]-7-methoxy-4,6-dimethyl-2,4-heptadienoic acid (11): Methyl ester **10** (0.06 mmol, 19 mg), LiOH (0.52

M (aq), 0.161 mL), and methanol (0.30 mL) were combined in a round-bottom flask equipped with a reflux condenser. The mixture was allowed to stir for 12 h at 45 ºC. The reaction was acidified to pH = 2 and stirred for an additional 10 min. The reaction mixture was then extracted with methylene chloride. The organic phases were combined and dried over Na_2SO_4. Solvent was removed *in vacuo* to yield sufficiently pure **11** (16 mg, 88%). This material was used without further purification as a ~2:1 mixture of *E*,*E* and *E*,*Z* isomers in the oxidation step: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 16.0 Hz, 1H), 7.45 (d, *J* = 16.0 Hz, 1H),7.12 (d, *J* = 8.5 Hz, 4H), 6.72 (d, *J* = 8.5 Hz, 4H), 5.93 (d, *J* = 9.0 Hz, 1H), 5.83 (d, *J* = 15.5 Hz, 1H), 5.79 (d, *J* = 15.5 Hz, 1H), 5.75 (d, *J* = 9.5 Hz, 1H), 3.89 (d, *J* = 7.0 Hz, 1H), 3.88 (d, *J* = 6.0 Hz, 1H), 3.16 (s, 3H), 3.16 (s, 3H), 3.06 (m, 1H), 2.97 (s, 6H), 2.96 (s, 6H), 2.86 (m, 1H), 1.89 (d, *J* = 1.5 Hz, 3H), 1.73 (d, *J* = 1.0 Hz, 3H), 0.88 (d, *J* = 5.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 172.6, 152.5, 150.4, 147.0, 146.9, 144.1, 144.0, 143.9, 132.9, 130.7, 128.6, 128.5, 127.9, 127.8, 117.3, 114.8, 112.5, 112.4, 88.3, 88.1, 56.9, 40.8, 40.7, 39.7, 29.7 20.3, (impurity), 18.2, 17.0, 17.0, 12.6; IR (film) 2975, 2928, 2819, 1685, 1614, 1522, 1350, 1283, 1104, 938, 817, 733 cm^{-1}; HRMS (FAB) for $C_{18}H_{26}NO_3$ $[M+H]^+$ calcd 304.1913, found 304.1911.



3

Trichostatic Acid (3): To a vial containing methoxycarboxylic acid **11** (16 mg, 0.053 mmol) was added methylene chloride (0.24 mL) and water (0.05 mL). This mixture was allowed to stir under open atmosphere while DDQ (13 mg, 0.058 mmol) was added as a

solid. More methylene chloride (0.50 mL) was added to wash the walls of the vial. The reaction mixture was stirred for 30 min. Methylene chloride (2 mL) was added, and the mixture was filtered through a pad of Celite. The resulting filtrate was dried over Na_2SO_4, and concentrated *in vacuo* to give crude product. The crude material was initially purified by flash chromatography (1:1 EtOAc/hexanes; silica). The *E*,*E*-isomer (5 mg, ~30% yield) was isolated by preparative HPLC (35→45% MeCN/H_2O [1 wt % NH_4OAc]). ^{1}H NMR (800 MHz, CD_3OD) δ 7.85 (d, *J* = 8.8 Hz, 2H, ArH meta to NMe_2), 7.01 (d, *J* = 16 Hz, 1H, H<u>C</u>=C-C=O), 6.72 (d, *J* = 8.8 Hz, 2H, ArH ortho to NMe_2), 5.92 (d, *J* = 16 Hz, 1H, C=C<u>H</u>-C=O), 5.74 (d, *J* = 8.8 Hz, 1H, C<u>H</u>=C-C=C-C=O), 4.52-4.48 (m, 1H, C<u>H</u>CH_3), 3.05 (s, 6H, N[C<u>H</u>$_3$]$_2$), 1.92 (d, *J* = 0.8, 3H, C=CC<u>H</u>$_3$), 1.24 (d, *J* = 7.2 Hz, 3H, CHC<u>H</u>$_3$); (lit.[9] ^{1}H NMR); ^{13}C NMR (HSQC-HMBC, 200 MHz, CD_3OD) 201.4 (Ar<u>C</u>OCH), 175.7 (<u>C</u>OOH), 155.0 (Ar ipso to NMe_2), 145.0 (<u>C</u>=C-C=O), 138.5 (<u>C</u>=C-C=C-C=O), 134.7 (C=<u>C</u>-C=C-C=O), 131.6 (Ar meta to NMe_2), 125.0 (C=<u>C</u>-C=O), 124.5 (Ar para to NMe_2), 111.5 (Ar ortho to NMe_2), 41.4 (<u>C</u>HCH_3), 39.8 (N[<u>C</u>H$_3$]$_2$), 17.8 (CH<u>C</u>H$_3$), 12.6 (C=C<u>C</u>H$_3$).

Determination of enantiomeric purity of trichostatic acid (3). Trichostatic acid **3** was treated with excess CH_2N_2 according to Mori[10] and the resulting soln was subjected to HPLC analysis (CHIRALCELL-OD; 5% *i*-PrOH in hexanes isocratic; 1mL/min). The retention time for (*R*)-**3** was 24.0 min, and (*S*)-**3** was 30.5 min. The measured ratio of (*R*)-**3** to (*S*)-**3** was 93:7.

[9] Hosokawa, S.; Ogura, T.; Togashi, H.; Tatsuta, K. *Tetrahedron Lett.* **2005**, *46*, 333.
[10] Mori, K.; Koskki, K. *Tetrahedron* **1988**, *44*, 6013.

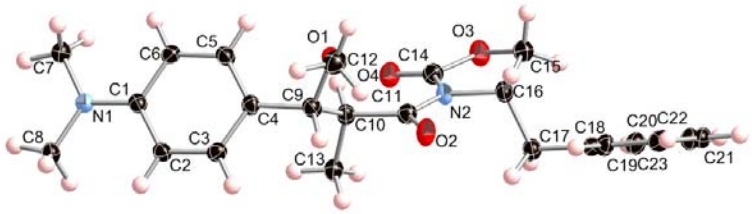


FIGURE S1. Crystal structure of **7**