Synthesis of (7*S*,15*S*)- and (7*R*,15*S*)-Dolatrienoic Acid[1a]

Jonathan J. Duffield and George R. Pettit*

Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, Tempe, Arizona 85287-2404

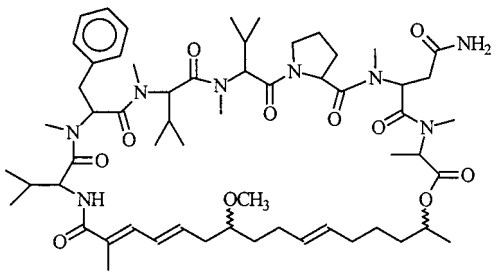
Received October 27, 2000

The stereospecific synthesis of (7*S*,15*S*)- and (7*R*,15*S*)-dolatrienoic acids (**2**) was achieved using an approach consisting of 16 linear steps. The C-11−C-16 unit was prepared in seven steps from ethyl (*S*)-lactate and coupled using a trans-selective Wittig−Schlosser reaction to the C-7−C-10 fragment. Chirality at the C-7 position was introduced using an Evan's-type chiral auxiliary in a cobalt-mediated Reformatsky reaction to give the (3*S*,11*S*)-aldehyde **24**. Subsequent Wittig reaction with a phosphonium salt derived in three steps from tiglic acid gave (7*S*,15*S*)-dolatrienoic acid, one of the four possible diastereoisomers of the nonpeptide portion of the strong cancer cell growth inhibitory cyclodepsipeptide dolastatin 14 (**1**). A second diastereoisomer, (7*R*,15*S*)-dolatrienoic acid, was synthesized employing chiral oxazolidinone **21** by an analogous synthetic route.

In 1972 we began to pursue the Indian Ocean sea hare *Dolabella auricularia* as an especially valuable source of structurally unique and exceptionally active anticancer constituents.[1b,2,3] Later, we isolated dolastatins 1−18 and elucidated the structures of dolastatins 3 and 10−18 from this shell-less mollusc.[3] The most promising of these, dolastatin 10, was isolated in 1984.[2] We completed the first total synthesis[4] to allow advanced preclinical and clinical development of this new anticancer drug, which is presently undergoing a series of phase II human cancer clinical trials under the auspices of the U.S. National Cancer Institute.

Results and Discussion

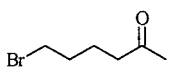
Dolastatin 14 was isolated (12 mg from 1600 kg of *D. auricularia* in 7.5×10^{-7}% yield) and assigned structure **1** on the basis of a series of high-field 2D NMR studies. Dolastatin 14 consists of a heptapeptide joined by a 16-carbon olefinic carboxylic acid designated dolatrienoic acid to form a cyclodepsipeptide. The stereochemical assignments and more extensive biological evaluation of this unusual peptide have been precluded by its trace occurrence in the natural source. However, dolastatin 14[2] (**1**)



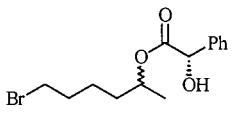
1, Dolastatin 14

was found to exhibit exceptional activity against a selection of human cancer cell lines.[3] Thus a practical, total synthesis of dolastatin 14 has become very necessary, and the present investigation was undertaken to begin addressing this research objective. We earlier assumed the stereochemistry of the dolastatin 14 heptapeptide unit to be exclusively *S* by comparison with other dolastatins from the same sea hare,[5] but no such ready comparison was apparent for the C-7 and C-15 chiral centers of dolatrienoic acid. Their absolute configurations need to be assigned by an X-ray crystal structure, which so far has eluded us, or by the total synthesis of dolastatin 14 and comparison with spectral data acquired from the natural product. Two (the 7*R*,15*R* and 7*S*,15*R*) of the four possible diastereoisomers were recently synthesized.[6] Now follows a summary of our syntheses of the 7*S*,15*S* and 7*R*,15*S* diastereoisomers of dolatrienoic acid by procedures suitable for preparation of the other two isomers.

Retrosynthetic analysis of dolatrienoic acid (**2**) initially led us to a disconnection at the C-6−C-7 bond (Scheme 1). The overall plan was based on a hexadiene ester of the type **3** undergoing a doubly vinylogous aldol reaction with the optically pure aldehyde **4**. We envisaged the preparation of aldehyde **4** from a suitably protected phosphonium salt **6** and the already known[7] aldehyde **5**. In turn the phosphonium salt **6** would be prepared from the alcohol **7**,[8] and the latter might be resolved by using an appropriate chiral auxiliary and fractional recrystallization. The approach just outlined was implemented by preparation of bromo alcohol **7** by sodium borohydride reduction of the ketone **8**, derived from ethyl acetoacetate according to the procedure of Curran and Scholz.[8] Esterification with (*S*)-mandelic acid gave the corresponding diastereomeric esters (**9**). Repeated fractional crystallization of the esters gave a low yield of the *S*,*S* isomer as a pure crystalline solid, but the *R*,*S* isomer resisted crystallization and purification.



8



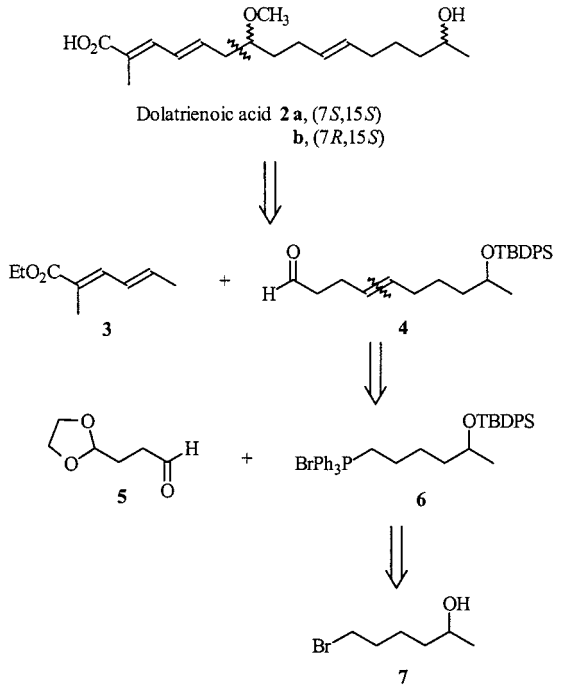
9 a, (*S*,*S*)
b, (*R*,*S*)

In view of these results a different route (Scheme 2) was chosen to obtain the chiral isomer of phosphonium salt **6**. Starting from the readily available ethyl (*S*)-lactate (**10**), TBDPS protection followed by reduction with borane gave alcohol **12**. An initial attempt to convert this directly to bromide **14** using *N*-bromosuccinimide and triphenylphos-

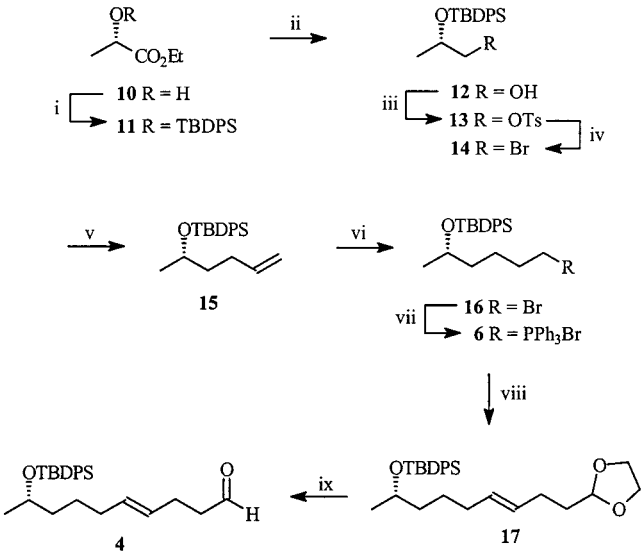
* To whom correspondence should be addressed. Tel: (480)-965-3351. Fax: (480)-965-8558.

10.1021/np000502q CCC: $20.00
Published on Web 04/06/2001

Scheme 1



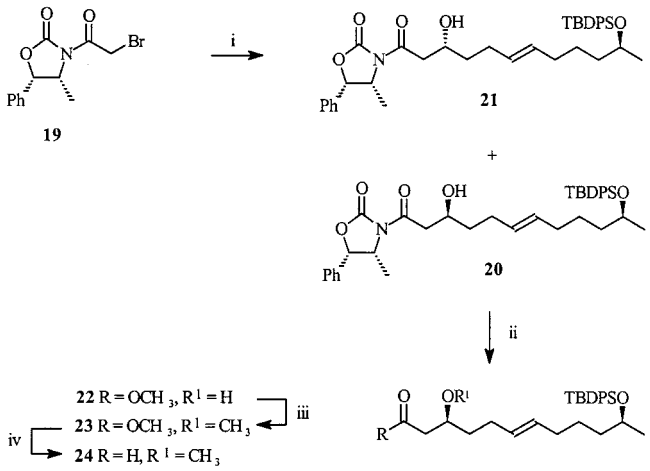
Scheme 2[a]



[a] (i) TBDPSCl, imidazole, DMF; (ii) BH_3·THF, THF, reflux; (iii) TsCl, pyridine, DCM; (iv) LiBr, THF, reflux; (v) allylmagnesium bromide, Li_2CuCl_4, THF; (vi) BH_3·THF, Br_2, $NaOCH_3$; (vii) PPh_3, toluene, reflux; (viii) PhLi, 1,3-dioxolane-2-propanal, PhLi, HCl, KO^{t}Bu; (ix) 30% aqueous acetic acid/THF, 1:1, reflux.

phine in DMF gave only a moderate yield of 55%. Finally the alcohol (**12**) was converted to bromide **14** via tosylate **13** with an overall yield for the two steps of 93%. Three-carbon homologation of bromide **14** was achieved by the lithium tetrachlorocuprate catalyzed addition of allylmagnesium bromide. The resulting olefin **15** underwent anti-Markovnikov bromination to give bromide **16**. On treatment with triphenylphosphine, the bromide **16** afforded the necessary chiral phosphonium salt **6**. The overall yield from ethyl (*S*)-lactate for the seven steps was 36%. Chiral aldehyde **4** was generated from phosphonium salt **6** utilizing the Schlosser modification of the Wittig reaction.[9] However, by allowing coupling between the ylid derived from phosphonium salt **6** and the aldehyde **5** under common Wittig reaction conditions (1 equiv of *n*-BuLi) both the *Z* and *E*

Scheme 3[a]



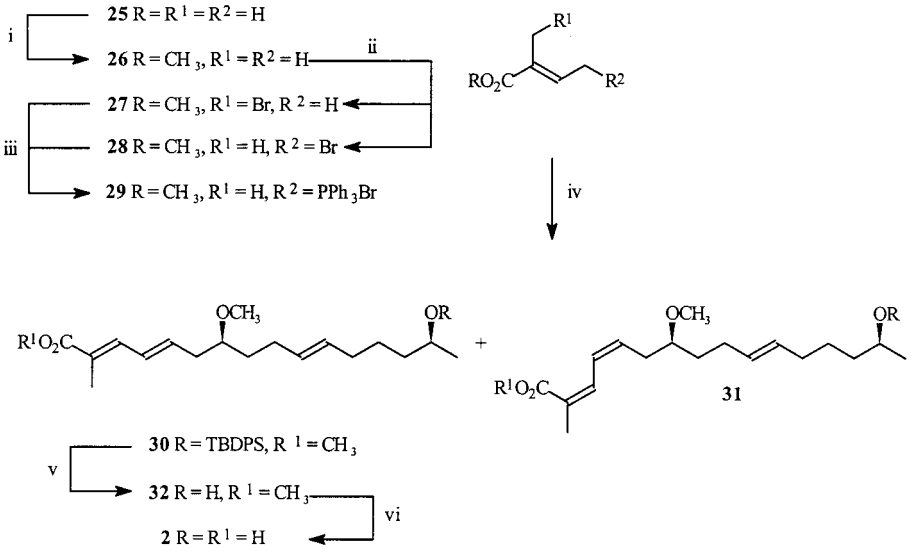
[a] (i) **4**, $Co(PPh_3)_4$, THF, 0 °C; (ii) CH_3OH, K_2CO_3, 0 °C, (iii) $(CH_3)_3OBF_4$, proton sponge, molecular sieves, DCM; (iv) DIBAL, DCM, then PDC, molecular sieves, DCM.

alkenes were formed in a ratio of about 9:1. When the Schlosser conditions were used, the selectivity of the reaction was reversed to give mostly the *E* alkene (**17**). The two isomers were easily separable by gravity Si gel column chromatography, and olefin **17** was converted to aldehyde **4** by treatment with aqueous acetic acid in THF. A small amount of the product was isolated as the C-9 alcohol (**18**) but was easily reprotected.

The proposed C-1−C-6 fragment (**3**) was prepared (90% yield) in one step by a Wadsworth−Emmons condensation between the commercially available triethylphosphonoacetate and crotonaldehyde. Attempts to couple diene **3** to aldehyde **4** via an aldol-type reaction were unsuccessful. Instead we utilized a new cobalt complex based Reformatsky reaction[10] involving the C-5−C-6 synthon **19** derived from (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone to give alcohol **20** (Scheme 3). We presumed the Evan's oxazolidinone approach would lead to good stereospecificity, but the reaction led to an approximately 1:1 mixture of alcohols (**20** and **21**). Fortunately, the presence of the chiral oxazolidinone group enabled the separation of the two diastereoisomers very simply by column chromatography. Once the oxazolidinone unit was removed by treatment with potassium carbonate in methanol, the 3*R*,11*S* and the 3*S*,11*S* diastereoisomers of ester **22** showed identical TLC. When the absolute stereochemistry of the natural product has been determined, the use of alternative chiral auxiliaries to achieve a stereospecific coupling reaction with aldehyde **4** will be investigated. The 3*S*,11*S* ester **22** was converted to the key intermediate **24** in two steps in an overall yield of 81%. The 3-hydroxyl position was first methylated using Meerwein's salt to give methyl ester **23**, which was subsequently reduced with DIBAL. Even at −78 °C the ester was rapidly reduced to an approximate 1:1 mixture of aldehyde **24** and the corresponding alcohol. Immediate treatment of this mixture with pyridinium dichromate in the presence of molecular sieves led to aldehyde **24**.

The 7*S*,15*S* diastereoisomer (**2a**) of dolatrienoic acid (**2**) was prepared by a simple Wittig reaction between aldehyde **24** and the phosphonium salt **29** prepared in three steps from tiglic acid (**25**) as follows. Methylation followed by vinylic bromination with *N*-bromosuccinimide gave a mixture of two bromo derivatives (**27** and **28**). While the two resisted separation by distillation or column chromatography, when the mixture was treated with triphenylphos-

Scheme 4[a]



[a] (i) Methanol, H_2SO_4, reflux; (ii) NBS, AIBN, CCl_4, reflux; (iii) PPh_3, toluene, reflux 2 h; (iv) 1 equiv of NaH rt then 1 equiv of **24** −78 °C→rt; (v) HF·pyridine, THF, 117 h; (vi) $LiOH·H_2O$, 1.3 equiv, THF/water 4:1, 160 h.

phine in refluxing toluene, only one product, the less hindered salt **29**, was isolated. Reaction between the ylid derived from phosphonium salt **29** (by treatment with sodium hydride) and aldehyde **24** gave rise to a mixture of diene **30** and its 4*Z* isomer (**31**). This mixture was converted to pure diene **30** by treatment with iodine in chloroform. Cleavage of the silyl-protecting group was first attempted using tetrabutylammonium fluoride, but this proved too basic and caused elimination of methanol to produce the corresponding very stable conjugated triene. Reaction of silyl ether **30** with aqueous HF was very slow, probably due to the biphasic system. Eventually it was found that deprotection using hydrogen fluoride/pyridine complex was most satisfactory, yielding alcohol **32** in 89% yield. Finally ester hydrolysis using lithium hydroxide gave (7*S*,15*S*)-dolatrienoic acid (**2a**) in 79% yield along with 14% of recovered starting material (Scheme 4). The 7*R*,15*S* diastereoisomer (**2b**) of dolatrienoic acid (**2**) was prepared from (4*R*,5*S*,3′*R*,11′*S*)-3-(11′-(*tert*-butyldiphenylsilyloxy)-3′-hydroxy-6′*E*-dodecenoyl)-4-methyl-5-phenyl-2-oxazolidinone (**21**), which is formed in approximately equal amounts as the 4*R*,5*S*,3′*S*,11′*S* isomer (**20**) during the cobalt-mediated Reformatsky reaction. The reactions performed are identical to those used to prepare the 7*S*,15*S* diastereoisomer of dolatrienoic acid. The configuration at C-3 for compounds **20** and **21** was determined by a comparison of the NMR spectra of **2a** and **2b** to the corresponding enantiomers of the Moune et al.[6] work, for which absolute configuration was determined.

In summary the first total syntheses of (7*S*,15*S*)-dolatrienoic (**2a**) acid and its 7*R*,15*S* isomer were completed employing a convergent procedure. The longest linear sequence required 16 steps and provided an overall yield from ethyl (*S*)-lactate of ∼1.5%. The 7*R*,15*S* diastereoisomer of dolatrienoic acid (**2b**) was prepared in six steps using analogous reactions from key intermediate **21**. We are now initiating synthesis of the two remaining diastereoisomers of dolatrienoic acid by the substitution of (*S*)-2-(*tert*-butyldiphenylsilyloxy)-1-propanol (**12**) by its *R* enantiomer, which has been prepared[11] by Nicolaou et al. in four steps from ethyl (*S*)-lactate. Also synthesis of the heptapeptide portion of dolastatin 14 (**1**) and its coupling to dolatrienoic acid (**2a**) is currently in progress.

Experimental Section

General Experimental Procedures. All reagents were used as received from Sigma-Aldrich Chemical Co., Acros Chemical Co., or E.M. Scientific, and solvents were distilled prior to use. Reactions requiring anhydrous conditions were conducted in a flame-dried, round-bottom flask, sealed with a rubber septum under an atmosphere of argon. Evaporation of solvents was performed under reduced pressure using a rotary evaporator, with an external bath temperature of 45 °C. For TLC procedures, Si gel GHLF Uniplates (Analtech, Inc.) were utilized. Solvents, except aqueous solutions, were dried over 4 Å molecular sieves. Column chromatography (Kieselgel 60) was performed using Si gel supplied by E. Merck (Darmstadt).

Melting points are uncorrected and were determined employing an Electrothermal 9100 apparatus. Optical rotations were recorded using a Perkin-Elmer 241 polarimeter, and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were obtained with a Nicolet FT-IR Model MX-1 unit. NMR spectra were recorded using a Varian Gemini 300 MHz instrument with residual nondeuterated solvent as an internal standard. The EIMS mass spectra were from a FINNIGAN-MAT 312 instrument (70 eV). Elemental analyses were determined by Galbraith Laboratories, Inc. (Knoxville, TN).

Ethyl 2(*S*)-(*tert*-Butyldiphenylsilyloxy)propionate (11).[11] To *tert*-butylchlorodiphenylsilane (27.48 g, 100 mmol) in dry DMF (200 mL) was added in one portion imidazole (13.62 g, 200 mmol). The solution was cooled in an ice bath and stirred for 15 min, after which ethyl (*S*)-lactate (**10**, 11.9 mL, 105 mmol) was added (dropwise). After warming to room temperature and stirring for 21 h the reaction was completed by heating to 60 °C for a further 6 h. Water (1.5 L) was added, and the mixture was extracted with hexane (4 × 150 mL). The combined hexane extract was dried, filtered, and concentrated under reduced pressure to leave a pale yellow oil (35.1 g, 98%): bp 158 °C (1 mm); ^{1}H NMR ($CDCl_3$) δ 7.67 (m, 4 H), 7.33−7.44 (m, 6 H), 4.26 (q, J = 6.7 Hz, 1 H), 4.02 (q, J = 7.2 Hz, 2 H), 1.39 (d, J = 6.7 Hz, 3 H), 1.14 (t, J = 7.2 Hz, 3 H), 1.11 (s, 9 H).

2(*S*)-(*tert*-Butyldiphenylsilyloxy)-1-propanol (12).[11] To the preceding (**11**, 35.1 g, 98.4 mmol) in anhydrous THF (100 mL) was added borane THF complex (1.0 M in THF, 200 mL) (dropwise). After completion of the addition the mixture was stirred at reflux for 2 h. The solution was cooled to room temperature and the reaction terminated by slow (dropwise) addition of water (100 mL). The THF was removed under reduced pressure, and the residue was extracted with DCM. The combined extract was dried, filtered, and concentrated

under reduced pressure to leave a colorless oil (30.85 g, 100%): bp 154 °C (1.25 mm); ^{1}H NMR ($CDCl_3$) δ 7.73 (m, 4 H), 7.38−7.46 (m, 6 H), 4.00 (m, 1 H), 3.55 (dd, J = 4.0, 12.1 Hz, 1 H), 3.44 (dd, J = 5.5, 12.1 Hz, 1 H), 2.02 (bs, 1H), 1.12 (s, 9 H), 1.09 (d, J = 7.6 Hz, 3 H).

2(*S*)-(*tert*-Butyldiphenylsilyloxy)-1-(4-methylbenzenesulfonyloxy)propane (13). To a solution of 2(*S*)-(*tert*-butyldiphenylsilyloxy)-1-propanol (**12**, 34.5 g, 110 mmol) in dry DCM (70 mL) was added (one portion) tosyl chloride (31.5 g, 165 mmol). The solution was cooled to 0 °C, and pyridine (17.8 mL, 220 mmol) was added (dropwise) with stirring. A white precipitate formed, and 30 min later the reaction was allowed to warm to room temperature and stirred for a further 24 h. The reaction was stopped with HCl (1.0 M, 200 mL). The organic layer was removed, and the aqueous phase was extracted with additional DCM. The combined organic extract was washed with sodium bicarbonate solution and brine, dried, filtered, and concentrated under reduced pressure to afford a pale yellow oil (64.42 g), which was a mixture of the required product (**13**) and tosyl chloride and used without further purification: bp 180 °C (0.06 mm); $[\alpha]^{27}_D$ −16.6 (*c* 1, $CHCl_3$); IR (NaCl) 3071, 2957, 1366, 1178, 1109 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 144.6, 135.8, 135.7, 133.7, 133.3, 132.9, 129.7, 127.9, 127.6, 127.5, 73.9, 67.0, 26.8, 21.6, 20.0, 19.0; ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.4 Hz, 2 H), 7.62 (m, 4 H), 7.28−7.47 (m, 8 H), 3.98 (sx, J = 5.6 Hz, 1 H), 3.92 (dd, J = 5.4, 9.3 Hz, 1 H), 3.83 (dd, J = 5.1, 9.3 Hz, 1 H), 2.45 (s, 3 H), 1.06 (d, J = 6.3 Hz, 3 H), 1.04 (s, 9 H); MS *m*/*z* (rel int) 411 (M^+ − 57, 23), 353 (100).

1-Bromo-2(*S*)-(*tert*-butyldiphenylsilyloxy)propane (14). Lithium bromide (19.14 g, 220 mmol) was added (in one portion) to 2(*S*)-(*tert*-butyldiphenylsilyloxy)-1-(4-methylbenzenesulfonyloxy)propane (**13**, 51.48 g, 110 mmol) in dry THF (110 mL). The solution was stirred and heated at reflux for 47 h, during which time a white precipitate formed. The mixture was cooled to room temperature, diluted with water, and extracted with DCM. The organic extract was dried, filtered, and concentrated under reduced pressure to a brown oily residue. Separation by gravity Si gel column chromatography (97:3 hexanes−EtOAc as eluent) led to a colorless oil (38.2 g, 93%): bp 162 °C (1.5 mm); $[\alpha]^{24}_D$ −14.8 (*c* 1, CH_2Cl_2); IR (NaCl) 3070, 2960, 1191, 1109 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 135.8, 133.9, 133.7, 129.8, 129.7, 127.7, 127.6, 68.8, 39.4, 26.9, 21.9, 19.2; ^{1}H NMR ($CDCl_3$) δ 7.70 (m, 4 H), 7.36−7.46 (m, 6 H), 4.01 (ddq, J = 6.6, 4.5, 6.0 Hz, 1 H), 3.33 (dd, J = 10.2, 4.5 Hz, 1 H), 3.26 (dd, J = 10.2, 6.6 Hz, 1 H), 1.24 (d, J = 6.0 Hz, 3 H), 1.09 (s, 9 H); MS *m*/*z* (rel int) 321 (M^+ − 57, 42), 319 (M^+ − 57, 43), 263 (100). Anal. Calcd for $C_{19}H_{25}BrOSi$: C, 60.47; H, 6.68. Found: C, 60.76; H, 6.92.

5(*S*)-(*tert*-Butyldiphenylsilyloxy)-1-hexene (15). To a solution of 1-bromo-2(*S*)-(*tert*-butyldiphenylsilyloxy)propane (**14**, 34.60 g, 92 mmol) in anhydrous THF (100 mL) was added a solution of lithium tetrachlorocuprate (0.1 M, 16 mL, 1.6 mmol) in THF. Allylmagnesium bromide (1.0 M solution in ether, 160 mL, 160 mmol) was next added over ∼1 h (dropwise) with cooling (cold water bath). A slight exotherm was observed. The brown solution was allowed to stir for 17 h at room temperature. The reaction was terminated by slow addition of saturated aqueous ammonium chloride solution and extracted with hexane. The combined extract was dried, filtered, and concentrated under reduced pressure to a yellow oil. Separation of the product by gravity Si gel column chromatography (98:2 hexanes−EtOAc as eluent) gave the silyl ether (**15**) as a colorless oil (23.6 g, 76%): bp 148 °C (1 mm); $[\alpha]^{25}_D$ −10.4 (*c* 1, $CHCl_3$); IR (NaCl) 3070, 3051, 2964, 1645, 1109 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 138.8, 135.9, 134.9, 134.5, 129.5, 129.4, 127.5, 127.4, 114.2, 69.1, 38.6, 29.5, 27.1, 23.2, 19.3; ^{1}H NMR ($CDCl_3$) δ 7.74−7.81 (m, 4 H), 7.39−7.51 (m, 6 H), 5.78 (ddt, J = 17.1, 9.9, 6.6 Hz, 1 H), 4.92−5.05 (m, 2 H), 3.96 (sx, J = 6.0 Hz, 1 H), 2.14 (dt, J = 7.9, 6.6 Hz, 2 H), 1.52−1.74 (m, 2 H), 1.15 (d, J = 6.0 Hz, 3 H), 1.14 (s, 9 H); MS *m*/*z* (rel int) 281 (M^+ −57, 43), 199 (100). Anal. Calcd for $C_{22}H_{30}OSi$: C, 78.05; H, 8.93. Found: C, 77.66; H, 9.14.

1-Bromo-5(*S*)-(*tert*-butyldiphenylsilyloxy)hexane (16). To a solution of 5(*S*)-(*tert*-butyldiphenylsilyloxy-1-hexene (**15**, 24.0 g, 71 mmol) in anhydrous THF (36 mL) at 0 °C was added borane THF complex (1.0 M solution in THF, 23.7 mL, 71.1 mmol of hydride) (dropwise). After 30 min the reaction was allowed to warm to room temperature and stirred for a further 30 min. Excess hydride was quenched with MeOH (0.47 mL), and the reaction was cooled again to −5 °C. Bromine (4.7 mL, 91 mmol) was added dropwise at a rate such that reaction temperature did not rise above 0 °C. Sodium methoxide (5.56 M solution in MeOH, 21.24 mL, 118 mmol) was next added (dropwise) keeping the reaction temperature below 5 °C. On completion of the addition the reaction was allowed to warm to room temperature and then terminated with sodium bicarbonate solution. The mixture was extracted with hexane, and the combined extract was dried, filtered, and concentrated under reduced pressure to a yellow oil. Separation of the product by gravity Si gel column chromatography (1.5% EtOAc−hexane as eluent) gave the required product (**16**) as a yellow oil (20.17 g, 68%): bp 151 °C (1 mm); $[\alpha]^{25}_D$ −14.5 (*c* 1, $CHCl_3$); IR (NaCl) 3071, 2961, 2932, 2857, 1260, 1130, 1065, 1038, 822, 702 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 135.9, 134.8, 134.5, 129.5, 129.4, 127.5, 127.4, 69.2, 38.4, 33.7, 32.8, 27.0, 23.8, 23.2, 19.2; ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 4 H), 7.39 (m, 6 H), 3.84 (sx, J = 6.0 Hz, 1 H), 3.30 (t, J = 6.8 Hz, 2 H), 1.72 (m, 2 H), 1.43 (m, 4 H), 1.07 (d, J = 6.0 Hz, 3 H), 1.05 (s, 9 H); MS *m*/*z* (rel int) 363 (M^+ − 57, 15), 361 (M^+ − 57, 16), 83 (100). Anal. Calcd for $C_{22}H_{31}BrOSi$: C, 62.99; H, 7.45. Found: C, 63.46; H, 7.59.

5(*S*)-(*tert*-Butyldiphenylsilyloxy)hexyltriphenylphosphonium Bromide (6). Triphenylphosphine (15.1 g, 57 mmol) was added in one portion to 1-bromo-5(*S*)-(*tert*-butyldiphenylsilyloxy)hexane (**16**, 20.1 g, 48 mmol) in dry toluene (60 mL), and the solution was stirred and heated at reflux for 48 h. After cooling to room temperature the toluene was removed under reduced pressure and the brown residue was refrigerated until it solidified. The glassy solid was triturated with ether (6 × 50 mL), and the insoluble portion was dried under high vacuum (0.04 mmHg) to afford the required phosphonium salt (**6**) as an off-white foam (24.46 g, 75%): $[\alpha]^{27}_D$ −7.5 (*c* 1, $CHCl_3$); IR (NaCl) 3053, 2961, 2930, 2891, 1437, 1111, 1028, 997, 923 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 135.5, 134.8, 134.6, 134.3, 133.4, 133.2, 130.4, 130.2, 129.2, 127.2, 127.2, 68.7, 38.2, 26.8, 25.7, 25.5, 22.8, 22.3, 18.9; ^{1}H NMR ($CDCl_3$) δ 7.66−7.85 (m, 15 H), 7.60 (m, 4 H), 7.26−7.39 (m, 6 H), 3.80 (sx, J = 5.8 Hz, 1 H), 3.60 (m, 2 H), 1.35−1.69 (m, 6 H), 1.01 (d, J = 6.0 Hz, 3 H), 0.99 (s, 9 H); MS *m*/*z* (rel int) 483 (100), 262 (53).

2-(8′(*S*)-(*tert*-Butyldiphenylsilyloxy)-3′*E*-nonenyl)-1,3-dioxolane (17). To a solution of 5(*S*)-(*tert*-butyldiphenylsilyloxy)hexyltriphenylphosphonium bromide (**6**, 24.4 g, 35.8 mmol) in anhydrous THF (50 mL) was added (dropwise) phenyllithium[12] (1.15 M solution in ether, 31.2 mL, 35.9 mmol), giving a dark orange color. The solution was stirred at room temperature for 20 min and then cooled to −78 °C. A solution of 1,3-dioxolane-2-propanal[7] (**5**, 5.12 g, 39.4 mmol) in anhydrous ether (30 mL) was added (dropwise) over 30 min, during which time the reaction was allowed to warm to −40 °C. The pale orange suspension was stirred at −40 °C for 20 min, and then additional phenyllithium (1.15 M solution in ether, 31.2 mL, 35.9 mmol) was added dropwise, giving a blood red color. The reaction was warmed to −30 °C and stirred for a further 20 min. A solution of hydrogen chloride in ether (1.0 M, 40 mL) was added (dropwise) followed by potassium *tert*-butoxide (6.02 g, 53.8 mmol) (one portion). After warming to room temperature the reaction was stirred for an additional 90 min. Water was added, and the mixture was extracted with DCM. The combined extract was dried, filtered, and concentrated under reduced pressure to give a brown oil. Separation by gravity Si gel column chromatography (24:1 hexanes−EtOAc as eluent) gave alkene **17** as a colorless oil (8.7 g, 54%): bp 161 °C (1 mm); $[\alpha]^{25}_D$ −17.0 (*c* 1, $CHCl_3$); IR (NaCl) 3071, 3049, 2931, 2888, 2859, 1473, 1427, 1136, 1111, 1036, cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 135.8, 134.9, 134.5, 130.7, 129.4, 129.3, 129.1, 127.4, 127.4, 104.1, 69.4, 64.8, 38.9, 33.8, 32.4, 27.0, 25.0, 23.2, 19.2; ^{1}H NMR ($CDCl_3$) δ 7.71 (m, 4 H), 7.36−7.46 (m, 6 H), 5.40 (m, 2H), 4.89 (t, J = 4.8 Hz, 1H) 3.83−4.00 (m, 4 H), 2.13 (m, 2 H), 1.90 (m, 2 H), 1.69−1.77 (m, 2 H), 1.09 (s, 9 H), 1.09

(hidden, 3 H); MS *m/z* (rel int) 451 ($M^+ - 1$, 2), 395 ($M^+ - 57$, 7), 199 (100). Anal. Calcd for $C_{28}H_{40}O_3Si$: C, 74.29; H, 8.91. Found: C, 74.15; H, 9.45.

9(*S*)-(*tert*-Butyldiphenylsilyloxy)-4*E*-decenal (4). To a solution of 2-(8′(*S*)-(*tert*-butyldiphenylsilyloxy)-3′*E*-nonenyl)-1,3-dioxolane (**17**, 8.00 g, 17.7 mmol) in THF (210 mL) was added aqueous acetic acid (30%, 210 mmol). The solution was stirred and heated at reflux for 47 h. After cooling to room temperature the reaction was neutralized with saturated aqueous sodium bicarbonate solution (~1.6 L), and the mixture was extracted with DCM (6 × 100 mL). The combined extract was dried, filtered, and concentrated under reduced pressure to a yellow oil. Separation by gravity Si gel column chromatography (24:1 hexanes−EtOAc as eluent) afforded 9(*S*)-hydroxy-4*E*-decenal (**18**) as a colorless oil (0.38 g, 13%) and the required silyl ether (**4**) as a colorless oil (5.75 g, 80%): bp 117 °C (0.07 mm); $[\alpha]^{22}_D$ −17.4 (*c* 1, $CHCl_3$); IR (NaCl) 3071, 2931, 2858, 1728, 1427, 1136, 821 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 202.2, 135.8, 134.8, 134.5, 131.8, 129.4, 129.3, 127.7, 127.4, 127.3, 69.4, 43.5, 38.9, 32.4, 27.1, 25.2, 25.0, 23.2, 19.3; ^1H NMR ($CDCl_3$) δ 9.75 (t, J = 1.7 Hz, 1 H), 7.68 (m, 4 H), 7.34−7.43 (m, 6 H), 5.37 (m, 2H), 3.84 (sx, J = 6.0 Hz, 1 H), 2.47 (m, 2 H), 2.31 (m, 2 H), 1.88 (m, 2 H), 1.28−1.50 (m, 4 H), 1.06 (d, J = 6.0 Hz, 3 H), 1.06 (s, 9 H); MS *m/z* (rel int) 351-($M^+ - 57$, 54), 199(100). Anal. Calcd for $C_{26}H_{36}O_2Si$: C, 76.42; H, 8.88. Found: C, 76.67; H, 9.24.

3-(1-Bromoacetyl)-4*R*-methyl-5*S*-phenyl-2-oxazolidinone (19). To a stirred solution of 4*R*-methyl-5*S*-phenyl-2-oxazolidinone (5.00 g, 28.2 mmol) in THF (40 mL) at −78 °C was added (dropwise) *n*-BuLi (2.5 M solution in hexanes, 12.4 mL, 31 mmol). The solution became dark red. After 20 min bromoacetyl bromide (3.05 mL, 35 mmol) was added (dropwise), turning the reaction yellow. After 1 h at −78 °C the reaction was warmed to room temperature and stirred for a further 3 h. The reaction was stopped with water and extracted with DCM. The combined extract was washed with 1 N sodium hydroxide and then brine, dried, filtered, and concentrated under reduced pressure to a brown oil. Separation by gravity Si gel column chromatography (9:1 hexanes−EtOAc as eluent) gave the required oxazolidinone (**19**) as a clear, colorless oil (6.31 g, 75%): bp 141 °C (0.07 mm); $[\alpha]^{25}_D$ +19.8 (*c* 2, $CHCl_3$); IR (NaCl) 3065, 3034, 2986, 2936, 1782, 1705, 1356, 1200, 1123, 1040, 970 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 165.8, 152.6, 132.9, 129.0, 128.8, 125.7, 79.5, 55.2, 28.4, 14.27; ^1H NMR ($CDCl_3$) δ 7.27−7.43 (m, 5 H), 5.73 (d, J = 7.5 Hz, 1 H), 4.76 (qn, J = 6.8 Hz, 1 H), 4.55 (d, J = 12.6 Hz, 1 H), 0.92 (d, J = 6.6 Hz, 3 H); MS *m/z* (rel int) 299 (M^+, 27), 297 (M^+, 30), 107 (100).

3-(11′*S*-(*tert*-Butyldiphenylsilyloxy)-3′*S*-hydroxy-6′*E*-dodecenoyl)-4*R*-methyl-5*S*-phenyl-2-oxazolidione (20). Magnesium turnings (2.16 g, 89 mmol) were washed in dry DCM (20 mL) for 1 h. The DCM was removed via syringe, and triphenylphosphine (3.82 g, 14.6 mmol) was added followed by anhydrous cobalt chloride (0.47 g, 3.65 mmol). THF (37.5 mL) was added, and the mixture was stirred at room temperature for 24 h, by which time it had become dark brown. The reaction was cooled to 0 °C, and a solution of 3-(1-bromoacetyl)-4*R*-methyl-5*S*-phenyl-2-oxazolidinone (**19**, 4.56 g, 15.3 mmol) and 9(*S*)-(*tert*-butyldiphenylsilyloxy)-4*E*-decenal (**4**, 6.24 g, 15.3 mmol) in THF (75 mL) was added dropwise over 3 h. After a further 10 min at 0 °C the reaction was terminated by addition of 0.1 N HCl (375 mL). The mixture was extracted with EtOAc (5 × 100 mL), and the combined extract was dried, filtered, and concentrated under reduced pressure to a brown oil. Separation of the products by gravity Si gel column chromatography (4:1 hexanes−EtOAc as eluent) afforded the 3′*R*,-11′*S* isomer (**21**) as a colorless oil (3.1 g, 32%). The title compound (**20**) was also obtained as a colorless oil (3.2 g, 34%): bp 282 °C (1.5 mm); $[\alpha]^{25}_D$ +14.2 (*c* 1.3, $CHCl_3$); IR (NaCl) 3445, 3071, 2960, 2932, 2857, 1786, 1699, 1471, 1427, 1371, 1350, 1219, 1111, 702 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 172.7, 153.0, 135.9, 135.0, 134.6, 133.1, 131.0, 129.4, 129.3, 128.9, 128.7, 127.4, 127.3, 125.6, 79.2, 69.5, 67.5, 54.7, 42.7, 38.9, 36.4, 32.5, 28.5, 27.0, 25.1, 23.2, 19.3, 14.5; ^1H NMR ($CDCl_3$) δ 7.68 (m, 4 H), 7.29−7.45 (m, 11 H), 5.66 (d, J = 7.2 Hz, 1 H), 5.37 (m, 2H), 4.77 (qn, J = 6.8 Hz, 1 H), 4.10 (m, 1 H), 3.84 (sx, J = 5.8 Hz, 1 H), 3.09 (m, 2 H), 2.99 (br s, 1 H), 2.12 (m, 2 H), 1.88 (m, 2 H), 1.31−1.71 (m, 6 H), 1.05 (d, J = 6.0 Hz, 3 H), 1.05 (s, 9 H), 0.91 (d, J = 6.6 Hz, 3 H); MS *m/z* (rel int) 570 ($M^+ - 57$, 24), 199 (100). Anal. Calcd for $C_{38}H_{49}NO_5Si \cdot 1/2H_2O$: C, 71.66; H, 7.91; N, 2.20. Found: C, 71.32; H, 8.06; N, 2.18.

Isomer 21: bp (260 °C (0.06 mm); $[\alpha]^{25}_D$ −10.1 (*c* 1.5, $CHCl_3$); IR (NaCl) 3445, 3071, 2959, 2932, 2857, 1786, 1697, 1456, 1427, 1371, 1195, 1111, 1037, 968 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 172.5, 153.0, 135.9, 135.0, 134.6, 133.1, 131.1, 129.4, 129.3, 128.9, 128.8, 127.4, 127.4, 125.6, 79.1, 69.5, 67.3, 54.7, 42.7, 38.9, 36.3, 32.5, 28.5, 27.0, 25.1, 23.2, 19.2, 14.6; ^1H NMR ($CDCl_3$) δ 7.68 (m, 4 H), 7.30−7.42 (m, 11 H), 5.68 (d, J = 7.2 Hz, 1 H), 5.37 (m, 2H), 4.78 (qn, J = 6.8 Hz, 1 H), 4.13 (m, 1 H), 3.84 (sx, J = 5.9 Hz, 1 H), 3.18 (dd, J = 17.7, 2.7 Hz, 1 H), 3.18 (dd, J = 17.5, 2.7 Hz, 1 H), 3.00 (dd, J = 17.5, 9.0 Hz, 1 H), 2.88 (br s, 1 H), 2.13 (m, 2 H), 1.88 (m, 2 H), 1.26−1.71 (m, 6 H), 1.05 (s, 9 H), 1.04 (d, J = 6.0 Hz, 3 H), 0.91 (d, J = 6.6 Hz, 3 H); MS *m/z* (rel int) 627 (M^+, 1), 570 ($M^+ - 57$, 15), 199 (100). Anal. Calcd for $C_{38}H_{49}NO_5Si \cdot 1/2H_2O$: C, 71.66; H, 7.91; N, 2.20. Found: C, 71.71; H, 7.94.

Methyl 11*S*-(*tert*-Butyldiphenylsilyloxy)-3*S*-hydroxy-6*E*-dodecenoate (22). A saturated (ca. 0.056 M) methanolic solution of potassium carbonate (10.5 mL, 0.59 mmol) was added (dropwise) over about 30 min to a solution of 3-(11′*S*-(*tert*-butyldiphenylsilyloxy)-3′*S*-hydroxy-6′*E*-dodecenoyl)-4*R*-methyl-5*S*-phenyl-2-oxazolidione (**20**, 1.00 g, 1.6 mmol) in anhydrous methanol (5 mL) at 0 °C. After completion of the addition the reaction was stirred for a further 30 min. The reaction was stopped with saturated aqueous ammonium chloride, and the mixture was extracted with DCM. The combined extract was dried, filtered, and concentrated under reduced pressure to leave a yellow oil. Separation by gravity Si gel column chromatography (82:18 hexanes−EtOAc as eluent) afforded the required ester as a colorless oil (0.58 g, 75%): $[\alpha]^{25}_D$ −8.5 (*c* 1.7, $CHCl_3$); IR (NaCl) 3447, 3071, 2932, 2858, 1736, 1429, 1109, 821 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 173.3, 135.8, 134.9, 134.5, 131.0, 129.4, 129.3, 129.2, 127.4, 127.3, 69.4, 67.4, 51.6, 41.1, 38.8, 36.3, 32.4, 28.5, 27.0, 25.0, 23.2, 19.2; ^1H NMR ($CDCl_3$) δ 7.67 (m, 4 H), 7.33−7.42 (m, 6 H), 5.36 (m, 2H), 4.00 (m, 1 H), 3.84 (sx, J = 5.6 Hz, 1 H), 3.69 (s, 3 H), 2.50 (dd, J = 16.2, 3.6 Hz, 1 H), 2.41 (dd, J = 16.2, 8.4 Hz, 1 H), 2.09 (m, 2 H), 1.88 (m, 2 H), 1.26−1.61 (m, 6 H), 1.05 (s, 9 H), 1.05 (hidden 3 H); MS *m/z* (rel int) 425 ($M^+ - 57$, 7), 199 (100). Anal. Calcd for $C_{29}H_{42}O_4Si$: C, 72.16; H, 8.77. Found: C, 72.11; H, 8.97.

Methyl 11*S*-(*tert*-Butyldiphenylsilyloxy)-3*S*-methoxy-6*E*-dodecenoate (23). To a solution of methyl 11*S*-(*tert*-butyldiphenylsilyloxy)-3*S*-hydroxy-6*E*-dodecenoate (**22**, 1.43 g, 2.97 mmol) in anhydrous DCM (22 mL) was added 4 Å molecular sieves (1.8 g). After stirring at room temperature for 20 min Proton Sponge (1.88 g, 8.8 mmol) and trimethyloxonium tetrafluoroborate (1.27 g, 8.6 mmol) were added. The solution was stirred at room temperature for a further 3 h, during which time a white precipitate formed and the reaction became yellow. The suspension was diluted with DCM and filtered through a sintered funnel. The solid was rinsed with more DCM, and the combined filtrate and washings were concentrated under reduced pressure to a yellow oil. Purification by gravity Si gel column chromatography (19:1 hexanes−EtOAc as eluent) afforded ester **23** as a clear, colorless oil (1.40 g, 95%): $[\alpha]^{25}_D$ −11.0 (*c* 1, $CHCl_3$); IR (NaCl) 3071, 2932, 2857, 1740, 1109, 822, 704 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 172.0, 135.8, 134.8, 134.5, 130.8, 129.3, 129.3, 129.2, 127.3, 127.3, 77.0, 69.3, 56.8, 51.4, 39.1, 38.8, 33.7, 32.4, 28.0, 26.9, 25.0, 23.1, 19.1; ^1H NMR ($CDCl_3$) δ 7.68 (m, 4 H), 7.32−7.40 (m, 6 H), 5.35 (m, 2H), 3.84 (sx, J = 5.9 Hz, 1 H), 3.66 (s, 3 H), 3.64 (m, 1 H), 3.33 (s, 3 H), 2.54 (dd, J = 15.0, 7.2 Hz, 1 H), 2.41 (dd, J = 15.0, 5.4 Hz, 1 H), 2.03 (m, 2 H), 1.88 (m, 2 H), 1.31−1.65 (m, 6 H), 1.05 (s, 9 H), 1.04 (hidden 3 H); MS *m/z* (rel int) 439 ($M^+ - 57$, 77), 135 (100). Anal. Calcd for $C_{30}H_{44}O_4Si$: C, 72.54; H, 8.93. Found: C, 72.63; H, 9.16.

11*S*-(*tert*-Butyldiphenylsilyloxy)-3*S*-methoxy-6*E*-dodecenal (24). A solution of di-*iso*-butylaluminum hydride

(1.0 M in DCM, 5.4 mL, 5.4 mmol) was added (dropwise) at −78 °C to a solution of methyl 11*S*-(*tert*-butyldiphenylsilyloxy)-3*S*-methoxy-6*E*-dodecenoate (**23**, 1.38 g, 2.78 mmol) in anhydrous DCM (17 mL). After 5 min the cold reaction mixture was poured into 1 N HCl (50 mL), and the organic layer removed. The aqueous phase was extracted with DCM, and the combined extract was dried, filtered, and concentrated under reduced pressure to a yellow oil. Proton NMR revealed this to be a mixture of aldehyde **24** and the corresponding alcohol. This mixture was dissolved in anhydrous DCM (17 mL) and powdered 4 Å molecular sieves (1.53 g), and PDC (1.53 g, 3.8 mmol) was added in one portion. The suspension was stirred at room temperature for 1 h, during which time it became dark brown. The thick suspension was diluted with DCM, filtered through Celite, and concentrated to a brown oil. Separation by gravity Si gel column chromatography (9:1 hexanes−EtOAc as eluent) gave aldehyde **24** as a colorless oil (1.10 g, 85%): bp 187 °C (0.05 mm); $[\alpha]^{25}_D$ −12.6 (*c* 1, $CHCl_3$); IR (NaCl) 3069, 2932, 2859, 1726, 1554, 1460, 1427, 1375, 1105 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 201.5, 135.8, 134.8, 134.5, 131.1, 129.4, 129.3, 129.1, 127.4, 127.3, 75.6, 69.4, 56.7, 47.8, 38.8, 33.7, 32.4, 28.0, 27.0, 25.0, 23.2, 19.2; ^1H NMR ($CDCl_3$) δ 9.78 (t, J = 2.1 Hz, 1 H), 7.68 (m, 4 H), 7.32−7.40 (m, 6 H), 5.34 (m, 2H), 3.84 (sx, J = 6.0 Hz, 1 H), 3.70 (qn, J = 5.4 Hz, 1 H), 3.33 (s, 3 H), 2.59 (ddd, J = 15.9, 6.6, 2.1 Hz, 1 H), 2.50 (ddd, J = 15.9, 5.1, 2.0 Hz, 1 H), 2.03 (m, 2 H), 1.88 (m, 2 H), 1.32−1.67 (m, 6 H), 1.05 (s, 9 H), 1.04 (hidden 3 H); MS *m*/*z* (rel int) 409 (M^+ − 57, 3), 199 (100). Anal. Calcd for $C_{29}H_{42}O_3Si$: C, 74.63; H, 9.07. Found: C, 74.61; H, 9.31.

3-Methoxycarbonyl-2*E*-butenyltriphenylphosphonium Bromide (29). To a solution of tiglic acid (**25**, 5.67 g, 57 mmol) in methanol (60 mL) was added concentrated sulfuric acid (1 mL), and the solution was stirred and heated at reflux for 15 h. After cooling to room temperature the reaction was basified to pH 9 with sodium bicarbonate solution and extracted with DCM. The combined extract was washed with brine, dried, filtered, and concentrated to a yellow liquid (5.7 g), which was used without further purification. The mixture containing ester **26** was dissolved in carbon tetrachloride (50 mL), and *N*-bromosuccinimide (8.2 g, 50 mmol) was added followed by AIBN (16 mg, 0.1 mmol). The suspension was stirred and heated at reflux for 18 h. After cooling to room temperature the mixture was filtered and concentrated to a brown oil. Purification by gravity Si gel column chromatography (97:3 hexanes−EtOAc as eluent) gave a mixture of isomeric bromides (**27** and **28**) as a colorless liquid (7.8 g). To the mixture in toluene (50 mL) was added triphenylphosphine (8.5 g, 32 mmol). The reaction was stirred and heated at reflux for 2 h and then cooled to room temperature. The phosphonium salt was collected and washed with ether to give a light brown solid (12.1 g, 47%) (overall from tiglic acid). The solid was recrystallized three times from ethanol−ether to leave phosphonium salt **29** as colorless plates (6.30 g, 24%): mp 172 °C (dec); IR (KBr disk) 3034, 2978, 2909, 2860, 1711, 1645, 1439, 1271, 1113, 1067, 883, 729, 687, 544, 507 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 166.2, 136.1, 135.9, 134.9, 133.3, 133.2, 130.1, 129.9, 125.0, 124.9, 117.6, 116.4, 51.7, 25.3, 24.6, 13.0; ^1H NMR ($CDCl_3$) δ 7.47−7.72 (m, 15 H), 6.44 (dt, J = 8.1, 7.2 Hz, 1 H), 4.76 (dd, J = 15.9, 8.1 Hz, 2 H), 3.46 (s, 3 H), 1.41 (d, J = 3.3 Hz, 3 H); MS *m*/*z* (rel int) 374 (M^+ − 81, 48), 262 (100). Anal. Calcd for $C_{24}H_{24}BrO_2P$: C, 63.31; H, 5.31; Br, 17.55; P, 6.80. Found: C, 63.13; H, 5.54; Br, 17.49; P, 6.91.

Methyl 15*S*-(*tert*-Butyldiphenylsilyloxy)-7*S*-methoxy-2-methyl-2*E*,4*E*,10*E*-hexadecatrienoate (30). To 3-methoxycarbonyl-2*E*-butenyltriphenylphosphonium bromide (**29**, 0.58 g, 1.22 mmol) and NaH (60% dispersion in oil, 49 mg, 1.22 mmol) was added THF (20 mL). The reaction mixture was stirred at room temperature for 2 h, over which time an intense orange color formed. The ylid was added slowly (dropwise) to a solution of 11*S*-(*tert*-butyldiphenylsilyloxy)-3*S*-methoxy-6*E*-dodecenal (**24**, 0.57 g, 1.22 mmol) in THF (12 mL) at −78 °C. The orange solution was allowed to warm to room temperature over 4 h, and stirring was continued for a further 16 h. The reaction was terminated with water, and the mixture extracted with DCM. The combined extract was dried, filtered, and concentrated under reduced pressure to a yellow oil. Purification by gravity Si gel column chromatography (93:7 hexanes−EtOAc as eluent) afforded a mixture of *E*,*E*-diene **30** and the 4*Z* isomer (**31**) as a clear colorless oil (0.46 mg, 67%). Also isolated was the starting material (**24**, 183 mg, 32%). The mixture of isomers (**30** and **31**) was dissolved in chloroform (20 mL), and iodine (0.21 g, 0.82 mmol) was added. The purple solution was stirred at room temperature for 24 h. The reaction mixture was washed with 10% aqueous sodium bisulfite solution (2 × 10 mL) and brine (10 mL). The organic phase was dried, filtered, and concentrated under reduced pressure to leave the diene **30** as a colorless oil (0.46 g, 67%): $[\alpha]^{26}_D$ −12.6 (*c* 1, $CHCl_3$); IR (NaCl) 3069, 3048, 2934, 2859, 1709, 1640, 1462, 1244, 1109, 704 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 169.0, 138.7, 138.5, 135.8, 134.9, 134.6, 130.7, 129.6, 129.4, 129.3, 127.9, 127.4, 127.3, 125.3, 79.7, 69.4, 56.7, 51.7, 38.9, 37.3, 33.6, 32.4, 28.3, 27.0, 25.1, 23.2, 19.2, 12.6; ^1H NMR ($CDCl_3$) δ 7.67 (m, 4 H), 7.32−7.40 (m, 6 H), 7.18 (d, J = 11.4 Hz, 1 H), 6.39 (dd, J = 15.1, 11.4 Hz, 1 H), 6.07 (dt, J = 15.1, 7.4 Hz, 1 H), 5.34 (m, 2 H), 3.84 (sx, J = 6.0 Hz, 1 H), 3.73 (s, 3 H), 3.33 (s, 3 H), 3.25 (qn, J = 5.6 Hz, 1 H), 2.39 (t, J = 6.3 Hz, 2 H), 2.04 (m, 2 H), 1.93 (s, 3 H), 1.88 (m, 2 H), 1.31−1.55 (m, 6 H), 1.05 (s 9 H), 1.03 (d, hidden, 3 H); MS *m*/*z* (rel int) 505 (M^+ − 57, 100). Anal. Calcd for $C_{35}H_{50}O_4Si \cdot 1/2H_2O$: C, 73.51; H, 8.99. Found: C, 73.65; H, 8.78.

Methyl 15*S*-Hydroxy-7*S*-methoxy-2-methyl-2*E*,4*E*,10*E*-hexadecatrienoate (32). To a stirred solution of methyl 15*S*-(*tert*-butyldiphenylsilyloxy)-7*S*-methoxy-2-methyl-2*E*,4*E*,6*E*-hexadecatrienoate (**30**, 0.26, 0.47 mmol) in anhydrous THF (25 mL) was added (dropwise) hydrogen fluoride pyridine complex (70%, 3.8 mL). After stirring at room temperature for 117 h the reaction was diluted with EtOAc and washed with saturated aqueous sodium bicarbonate solution and then saturated aqueous ammonium chloride solution. The organic phase was dried, filtered, and concentrated under reduced pressure to a yellow oil. Separation by gravity Si gel column chromatography (4:1 hexanes−EtOAc as eluent) afforded the alcohol **32** as a clear colorless oil (0.14 g, 89%): $[\alpha]^{25}_D$ −1.7 (*c* 1.6, $CHCl_3$); IR (NaCl) 3450, 3030, 2930, 2857, 1709, 1640, 1435, 1244, 1107, 972 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 169.0, 138.7, 138.5, 130.5, 129.8, 127.9, 125.2, 79.7, 67.8, 56.6, 51.6, 38.7, 37.2, 33.5, 32.4, 28.2, 25.6, 23.4, 12.5; ^1H NMR ($CDCl_3$) δ 7.17 (d, J = 11.4 Hz, 1 H), 6.39 (dd, J = 15.0, 11.3 Hz, 1 H), 6.07 (dt, J = 15.0, 7.4 Hz, 1 H), 5.41 (m, 2 H), 3.77 (m, 1 H), 3.75 (s, 3 H), 3.34 (s, 3 H), 3.26 (qn, J = 5.9 Hz, 1 H), 2.39 (t, J = 6.3 Hz, 2 H), 2.01 (m, 4 H), 1.93 (s, 3 H), 1.36−1.60 (m, 6 H), 1.18 (d, J = 6.0 Hz, 3 H); MS *m*/*z* (rel int) 324 (M^+, 2), 292 (M^+ − 32, 5), 67 (100). Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94. Found: C, 70.05; H, 10.26.

15*S*-Hydroxy-7*S*-methoxy-2-methyl-2*E*,4*E*,10*E*-hexadecatrienoic Acid (2a). To a solution of methyl 15*S*-hydroxy-7*S*-methoxy-2-methyl-2*E*,4*E*,6*E*-hexadecatrienoate (**32**, 0.14 g, 0.42 mmol) in THF (7.5 mL) and water (1.9 mL) was added lithium hydroxide monohydrate (24 mg, 0.56 mmol) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 160 h. The mixture was acidified to pH 2 with 2 M HCl, diluted with water, and extracted with DCM. The combined extract was dried, filtered, and concentrated under reduced pressure to a yellow oil. Separation by gravity Si gel column chromatography afforded the starting material (**32**) as a colorless oil (19 mg, 14%, following elution with 4:1 hexanes−EtOAc) and the acid **2a** as a colorless oil (103 mg, 79%, by elution with 4:1 DCM−CH_3OH): $[\alpha]^{25}_D$ −1.4 (*c* 1, $CHCl_3$); IR (NaCl) 3422, 3135, 2930, 2859, 1682, 1422, 1260, 1103, 974, 814 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 173.5, 140.2, 139.7, 130.5, 129.9, 128.0, 124.8, 79.7, 68.0, 56.7, 38.7, 37.3, 33.6, 32.4, 28.3, 25.6, 23.4, 12.2; ^1H NMR ($CDCl_3$) δ 7.26 (d, J = 11.4 Hz, 1 H), 6.39 (dd, J = 15.0, 11.4 Hz, 1 H), 6.10 (dt, J = 15.0, 7.4 Hz, 1 H), 5.41 (m, 2 H), 3.79 (m, 1 H), 3.34 (s, 3 H), 3.26 (qn, J = 6.0 Hz, 1 H), 2.40 (t, J = 6.0 Hz, 2 H), 2.01 (m, 4 H), 1.92 (s, 3 H), 1.39−1.53 (m, 6 H), 1.18 (d, J = 6.0 Hz, 3 H); MS *m*/*z* (rel int) 292 (M^+ − 18, 3), 67 (100); HRMS *m*/*z* calcd for $C_{18}H_{30}O_4Na$, $(M + Na)^+$, 333.2042; found, $(M + Na)^+$, 333.2054.

Methyl 11*S*-(*tert*-Butyldiphenylsilyloxy)-3*R*-hydroxy-6*E*-dodecenoate (22b). A saturated (ca. 0.056 M) methanolic

solution of potassium carbonate (26.5 mL, 1.48 mmol) was added (dropwise) over about 30 min to a solution of 3-(11′*S*-(*tert*-butyldiphenylsilyloxy)-3′*R*-hydroxy-6′*E*-dodecenoyl)-4*R*-methyl-5*S*-phenyl-2-oxazolidione (**21**, 2.50 g, 3.99 mmol) in anhydrous methanol (5 mL) at 0 °C. After completion of the addition the reaction mixture was stirred for a further 30 min. The reaction was stopped with saturated aqueous ammonium chloride, and the mixture was extracted with DCM. The combined extract was dried, filtered, and concentrated under reduced pressure to leave a yellow oil. Separation by gravity Si gel column chromatography (82:18 hexanes−EtOAc as eluent) gave the required ester as a colorless oil (1.32 g, 69%): $[\alpha]^{25}_D$ −23.5 (*c* 1, $CHCl_3$); IR (NaCl) 3396, 3071, 2932, 2857, 1734, 1427, 1375, 1109, 822 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 173.3, 135.8, 134.9, 134.6, 131.0, 129.4, 129.3, 129.3, 127.4, 127.3, 69.4, 67.5, 51.6, 41.1, 38.8, 36.3, 32.4, 28.5, 27.0, 25.0, 23.2, 19.2; ^1H NMR ($CDCl_3$) δ 7.67 (m, 4 H), 7.32−7.41 (m, 6 H), 5.35 (m, 2H), 4.00 (m, 1 H), 3.84 (sx, J = 5.8 Hz, 1 H), 3.69 (s, 3 H), 2.50 (dd, J = 16.0, 3.6 Hz, 1 H), 2.41 (dd, J = 16.0, 8.4 Hz, 1 H), 2.09 (m, 2 H), 1.87 (m, 2 H), 1.30−1.59 (m, 6 H), 1.05 (s, 9 H), 1.05 (hidden 3 H); MS *m*/*z* (rel int) 425 (M^+ − 57, 4), 199 (100). Anal. Calcd for $C_{29}H_{42}O_4Si$: C, 72.16; H, 8.77. Found: C, 72.68; H, 9.00.

Methyl 11*S*-(*tert*-Butyldiphenylsilyloxy)-3*R*-methoxy-6*E*-dodecenoate (23b). After adding 4 Å molecular sieves (1.36 g) to a solution of methyl 11*S*-(*tert*-butyldiphenylsilyloxy)-3*R*-hydroxy-6*E*-dodecenoate (**22b**, 1.30 g, 2.7 mmol) in anhydrous DCM (20 mL) and stirring at room temperature for 20 min, Proton Sponge (1.71 g, 8.0 mmol) and trimethyloxonium tetrafluoroborate (1.15 g, 7.8 mmol) were added. The solution was stirred at room temperature for a further 3 h, during which time a white precipitate formed and the reaction mixture became yellow. The suspension was diluted with DCM and filtered through a sintered funnel. The solid was rinsed with more DCM, and the combined filtrate and washings were concentrated under reduced pressure to a yellow oil. Purification by gravity Si gel column chromatography (19:1 hexanes−EtOAc as eluent) afforded ester **23b** as a clear, colorless oil (1.33 g, 99%): $[\alpha]^{27}_D$ −16.9 (*c* 1, $CHCl_3$); IR (NaCl) 3071, 2932, 2859, 1742, 1429, 1375, 1109, 704 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 172.0, 135.8, 134.8, 134.5, 130.8, 129.3, 129.3, 129.2, 127.4, 127.3, 77.1, 69.4, 56.9, 51.4, 39.1, 38.8, 33.7, 32.4, 28.0, 26.9, 25.0, 23.1, 19.1; ^1H NMR ($CDCl_3$) δ 7.68 (m, 4 H), 7.33−7.40 (m, 6 H), 5.35 (m, 2H), 3.85 (sx, J = 5.5 Hz, 1 H), 3.69 (s, 3 H), 3.64 (m, 1 H), 3.34 (s, 3 H), 2.54 (dd, J = 15.0, 7.4 Hz, 1 H), 2.41 (dd, J = 15.0, 5.6 Hz, 1 H), 2.04 (m, 2 H), 1.88 (m, 2 H), 1.27−1.65 (m, 6 H), 1.06 (s, 9 H), 1.05 (hidden 3 H); MS *m*/*z* (rel int) 439 (M^+ − 57, 17), 199 (100). Anal. Calcd for $C_{30}H_{44}O_4Si$: C, 72.54; H, 8.93. Found: C, 72.95; H, 9.21.

11*S*-(*tert*-Butyldiphenylsilyloxy)-3*R*-methoxy-6*E*-dodecenal (24b). A solution of di-*iso*-butylaluminum hydride (1.0 M in DCM, 0.48 mL, 0.48 mmol) was added (dropwise) at −78 °C to a solution of methyl 11*S*-(*tert*-butyldiphenylsilyloxy)-3*R*-methoxy-6*E*-dodecenoate (**23b**, 0.12 g, 0.12 mmol) in anhydrous DCM (5 mL). After 5 min the cold reaction mixture was poured into 1 N HCl (20 mL), and the organic layer was removed. The aqueous phase was extracted with DCM, and the combined extract was dried, filtered, and concentrated under reduced pressure to a yellow oil. Proton NMR revealed this to be a mixture of aldehyde **24b** and the corresponding alcohol. The product was dissolved in anhydrous DCM (5 mL), and a mixture of powdered 4 Å molecular sieves (0.14 g) and PDC (0.14 g, 0.34 mmol) was added in one portion. The suspension was stirred at room temperature for 1 h, during which time it became dark brown. The thick suspension was diluted with DCM, filtered through Celite, and concentrated to a brown oil. Separation by gravity Si gel column chromatography gave aldehyde **24b** as a colorless oil (98 mg, 87%): bp 184 °C (0.06 mm); $[\alpha]^{25}_D$ −19.6 (*c* 1, $CHCl_3$); IR (NaCl) 3069, 2932, 2859, 1726, 1460, 1429, 1373, 1107 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 201.4, 135.8, 134.9, 134.5, 131.1, 129.4, 129.3, 129.1, 127.4, 127.4, 75.7, 69.4, 56.7, 47.9, 38.9, 33.7, 32.4, 28.0, 27.0, 25.0, 23.2, 19.2; ^1H NMR ($CDCl_3$) δ 9.79 (t, J = 2.2 Hz, 1 H), 7.68 (m, 4 H), 7.33−7.41 (m, 6 H), 5.34 (m, 2H), 3.84 (sx, J = 5.6 Hz, 1 H), 3.70 (qn, J = 6.1 Hz, 1 H), 3.34 (s, 3 H), 2.61 (ddd, J = 16.2, 6.9, 2.2 Hz, 1 H), 2.51 (ddd, J = 16.2, 5.3, 2.2 Hz, 1 H), 2.03 (m, 2 H), 1.88 (m, 2 H), 1.29−1.72 (m, 6 H), 1.05 (s, 9 H), 1.04 (hidden 3 H); MS *m*/*z* (rel int) 409 (M^+ − 57, 3), 199 (100). Anal. Calcd for $C_{29}H_{42}O_3Si$: C, 74.63; H, 9.07. Found: C, 74.26; H, 9.36.

Methyl 15*S*-(*tert*-Butyldiphenylsilyloxy)-7*R*-methoxy-2*E*,4*E*,10*E*-hexadecatrienoate (30b). To 3-methoxycarbonyl-2*E*-butenyltriphenylphosphonium bromide (**29**, 96 mg, 0.21 mmol) and NaH (60% dispersion in oil, 8.4 mg, 0.21 mmol) was added THF (3.5 mL). The reaction was stirred at room temperature for 2 h, over which time an intense orange color formed. The ylid was added slowly (dropwise) to a solution of 11*S*-(*tert*-butyldiphenylsilyloxy)-3*R*-methoxy-6*E*-dodecenal (**24b**, 98 mg, 0.21 mmol) in THF (2 mL) at −78 °C. The orange solution was allowed to warm to room temperature over 4 h, and stirring was continued for a further 16 h. The reaction was terminated with water, and the mixture was extracted with DCM. The combined extract was dried, filtered, and concentrated under reduced pressure to a yellow oil. Purification by gravity Si gel column chromatography (93:7 hexanes−EtOAc as eluent) afforded a mixture of *E*,*E*-diene (**30b**) and the 4*Z* isomer (**31b**) as a clear, colorless oil (77 mg, 65%). Also isolated was significant starting material (**24b**, 26 mg, 26%). The mixture of isomers (**30b** and **31b**) was dissolved in chloroform (7 mL), and iodine (35 mg, 0.138 mmol) was added. The purple solution was stirred at room temperature for 24 h. The reaction mixture was washed with 10% aqueous sodium bisulfite solution (2 × 10 mL) and brine (10 mL). The organic phase was dried, filtered, and concentrated under reduced pressure to leave the diene **30b** as a colorless oil (77 mg, 65%): $[\alpha]^{26}_D$ −11.8 (*c* 1.3, $CHCl_3$); IR (NaCl) 3069, 3042, 2934, 2859, 1709, 1640, 1432, 1242, 1107, 972, 824 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 169.0, 138.7, 138.5, 135.8, 134.9, 134.6, 130.8, 129.6, 129.4, 129.3, 128.0, 127.4, 127.3, 125.3, 79.7, 69.5, 56.7, 51.7, 38.9, 37.3, 33.6, 32.5, 28.3, 27.0, 25.1, 23.2, 19.2, 12.6; ^1H NMR ($CDCl_3$) δ 7.67 (m, 4 H), 7.32-;7.40 (m, 6 H), 7.18 (d, J = 11.5 Hz, 1 H), 6.39 (dd, J = 15.2, 11.5 Hz, 1 H), 6.07 (dt, J = 15.2, 7.4 Hz, 1 H), 5.34 (m, 2 H), 3.84 (sx, J = 5.8 Hz, 1 H), 3.74 (s, 3 H), 3.34 (s, 3 H), 3.24 (qn, J = 6.0 Hz, 1 H), 2.39 (t, J = 6.6 Hz, 2 H), 2.04 (m, 2 H), 1.93 (s, 3 H), 1.89 (m, 2 H), 1.31−1.54 (m, 6 H), 1.05 (s 9 H), 1.04 (d, hidden, 3 H); MS *m*/*z* (rel int) 505 (M^+ − 57, 8), 199 (100); HRMS *m*/*z* calcd for $C_{34}H_{41}O_4Si$, $(M - C_4H_9)^+$, 505.2774; found, $(M - C_4H_9)^+$, 505.2780.

Methyl 15*S*-Hydroxy-7*R*-methoxy-2-methyl-2*E*,4*E*,10*E*-hexadecatrienoate (32b). To a stirred solution of methyl 15*S*-(*tert*-butyldiphenylsilyloxy)-7*R*-methoxy-2-methyl-2*E*,4*E*,6*E*-hexadecatrienoate (**30b**, 61 mg, 0.11 mmol) in anhydrous THF (6 mL) was added (dropwise) hydrogen fluoride pyridine complex (70%, 0.9 mL). After stirring at room temperature for 88 h the reaction was diluted with EtOAc and washed with saturated aqueous sodium bicarbonate solution and then saturated aqueous ammonium chloride solution. The organic phase was dried, filtered, and concentrated under reduced pressure to a yellow oil. Separation by gravity Si gel column chromatography (4:1 hexanes−EtOAc as eluent) provided the alcohol **32b** as a clear colorless oil (0.14 g, 89%): $[\alpha]^{27}_D$ +8.0 (*c* 1.2, $CHCl_3$); IR (NaCl) 3412, 3027, 2930, 2857, 1707, 1640, 1437, 1244, 1105, 972 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 169.0, 138.7, 138.5, 130.5, 129.9, 128.0, 125.3, 79.8, 68.0, 56.7, 51.7, 38.8, 37.3, 33.6, 32.4, 28.3, 25.6, 23.5, 12.6; ^1H NMR ($CDCl_3$) δ 7.17 (d, J = 11.2 Hz, 1 H), 6.39 (dd, J = 15.0, 11.2 Hz, 1 H), 6.07 (dt, J = 15.0, 7.4 Hz, 1 H), 5.41 (m, 2 H), 3.78 (m, 1 H), 3.75 (s, 3 H), 3.34 (s, 3 H), 3.26 (qn, J = 6.0 Hz, 1 H), 2.39 (t, J = 6.6 Hz, 2 H), 2.01 (m, 4 H), 1.93 (s, 3 H), 1.40−1.55 (m, 6 H), 1.19 (d, J = 6.0 Hz, 3 H); MS *m*/*z* (rel int) 324 (M^+, 1), 292 (M^+ − 32, 4), 67 (100); HRMS *m*/*z* calcd for $C_{19}H_{32}O_4$, (M^+), 324.2301; found, (M^+), 324.2313.

15*S*-Hydroxy-7*R*-methoxy-2-methyl-2*E*,4*E*,10*E*-hexadecatrienoic acid (2b). To a solution of methyl 15*S*-hydroxy-7*R*-methoxy-2-methyl-2*E*,4*E*,6*E*-hexadecatrienoate (**32b**, 20 mg, 0.062 mmol) in THF (1.1 mL) and water (0.28 mL) was added lithium hydroxide monohydrate (3.5 mg, 0.083 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 90 h. Following acidification to

pH 2 with 2 M HCl and dilution with water, the solution was extracted with DCM. The combined extract was dried, filtered, and concentrated under reduced pressure to a yellow oil. Separation by gravity Si gel column chromatography afforded the starting material (**32b**) as a colorless oil (3.5 mg, 18%, elution with 4:1 hexanes−EtOAc) and the acid **2b** as a colorless oil (15 mg, 79%, elution with 4:1 DCM−CH_3OH): $[\alpha]^{27}_D$ +6.4 (*c* 1.5, $CHCl_3$); IR (NaCl) 3414, 2930, 2857, 1682, 1640, 1422, 1377, 1254, 1105, 974, 812, 750 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 173.3, 140.4, 139.8, 130.5, 129.9, 128.0, 124.7, 79.7, 68.0, 56.8, 38.7, 37.3, 33.6, 32.4, 28.3, 25.6, 23.4, 12.2; ^1H NMR ($CDCl_3$) δ 7.28 (d, J = 11.1 Hz, 1 H), 6.41 (dd, J = 14.8, 11.1 Hz, 1 H), 6.12 (dt, J = 14.8, 7.8 Hz, 1 H), 5.41 (m, 2 H), 3.80 (m, 1 H), 3.35 (s, 3 H), 3.27 (qn, J = 5.9 Hz, 1 H), 2.41 (t, J = 6.5 Hz, 2 H), 2.02 (m, 4 H), 1.93 (s, 3 H), 1.36−1.60 (m, 6 H), 1.19 (d, J = 6.0 Hz, 3 H); MS *m*/*z* (rel int) 292 (M^+ − 18, 3), 67 (100); HRMS *m*/*z* calcd for $C_{18}H_{30}O_4Na$, $(M + Na)^+$, 333.2042; found, $(M + Na)^+$, 333.2033.

Acknowledgment. We very much appreciate the financial support provided by the following: Outstanding Investigator Grant CA44344-06-12 awarded by the Division of Cancer Treatment and Diagnosis, National Cancer Institute, DHHS; The Arizona Disease and Control Research Commission; Gary L. and Diane R. Tooker; Lottie Flugel; John and Edith Reyno; Dr. John Budzinski; Polly Trautman; the Ladies Auxiliary to the Veterans of Foreign Wars; and the Robert E. Dalton Endowment Fund.

References and Notes

(1) (a) Contribution 448 in the series *Antineoplastic Agents*. For part 447 see: Beutler, J. A.; McCall, K. L.; Herbert, K.; Herald, D. L.; Pettit, G. R.; Johnson, T.; Shoemaker, R. H.; Boyd, M. R. *J. Nat. Prod.* **2000**, *63*, 657−661. (b) Pettit, G. R.; Ode, R. H.; Herald, C. L.; Von Dreele, R. B.; Michel, C. *J. Am. Chem. Soc.* **1976**, *98*, 4677−4678.

(2) Pettit, G. R.; Kamono, Y.; Herald, C. L.; Tuinman, A. A.; Boetner, F. E.; Kizu, H.; Schmidt, J. M.; Baczynskyj, L.; Tomer, K. B.; Bontems, R. J. *J. Am. Chem. Soc.* **1987**, *109*, 6883−6885. Pettit, G. R. The Dolastatins. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C., Eds.; 1997; Vol. 70, pp 1−79.

(3) (a) Pettit, G. R. *Anticancer Drugs from Animals, Plants and Microorganisms*; J. Wiley and Sons: New York, 1994. (b) Pettit, G. R.; Xu, J.; Boyd, M. R. *J. Nat. Prod.* **1997**, *60*, 752−754. (c) Pettit, G. R.; Xu, J.; Cerny, R. L. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 827−832.

(4) Pettit, G. R.; Singh, S. B.; Hogan, F.; Lloyd-Williams, P.; Burkett, D. D.; Clewlow, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 5463−5465.

(5) Pettit, G. R.; Kamono, Y.; Herald, C. L.; Dufresne, C.; Bates, B. R.; Schmidt, J. M.; Cerny, R. L.; Kizu, H. *J. Org. Chem.* **1990**, *55*, 2989−2990.

(6) Moune, S.; Niel, G.; Busquet, M.; Eggleston, E.; Jouin, P. *J. Org. Chem.* **1997**, *62*, 3332−3339.

(7) Lucchesini, F. *Tetrehedron* **1992**, 9951−9966.

(8) Curran, D. P.; Scholz, D. *Monatsh. Chem.* **1977**, 1401−1411.

(9) Schlosser, M.; Christmann, K. F. *Angew. Chem.* **1966**, *78*, 115.

(10) Orsini, F. *J. Org. Chem.* **1997**, *62*, 1159−1163.

(11) Nicolaou, K. C.; Randall, J. L.; Furst, G. T. *J. Am. Chem. Soc.* **1985**, *107*, 5556−5558.

(12) Phenyllithium was freshly prepared before each reaction by the addition of an ethereal solution of bromobenzene to 2 equiv of lithium in ether. Excess lithium was removed by filtration through glass wool under an argon atmosphere. The solution was titrated against diphenylacetic acid.

NP000502Q