SYNTHETIC COMMUNICATIONS, 30(19), 3617–3628 (2000)

EFFICIENT SYNTHESIS OF THE C1-C8 FRAGMENT OF REVEROMYCINS

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Abstract: A stereocontrolled synthesis of the C1-C8 fragment of reveromycins is presented herein. Key to our strategy was the implementation of Evans' aldol reaction that delivered the desired stereochemistry at the C4 and C5 stereocenters.

Reveromycins A-D (**1-4**, Figure 1) are novel polyketide-type natural products that have been isolated recently from *Streptomyces* sp. and display attractive chemical structures[1] and biological profiles.[2] On the biological front these natural products exhibit impressive antiproliferative and antitumor activities, which presumably stem from inhibition of the epidermal growth factor (EGF)-mediated signal transduction.[3] In addition, reveromycins A, C and D inhibit protein synthesis selectively in eukaryotic cells and induce morphological reversion of scr^{ts}-NRK cells.[1] Equally intriguing is the structural motif of reveromycins, that is comprised of an identical C1-C24 backbone folded in such a way as to create a [6,6] or [5,6] spiroketal ring decorated with a hemisuccinate ester, two alkyl groups and two highly unsaturated side-chains.

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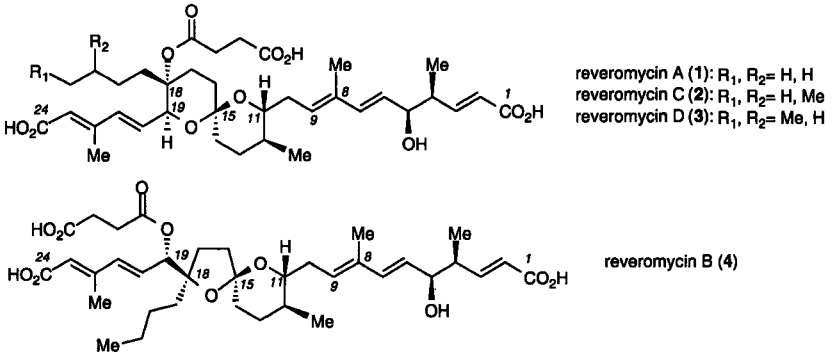
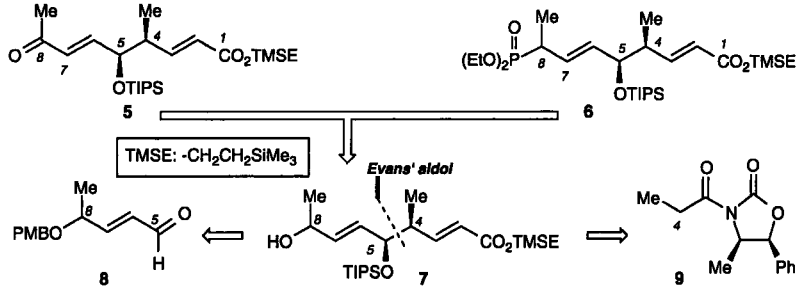
FIGURE 1



The combination of novel structures, intriguing biological activities and limited bioavailability manifested by reveromycins has captured the interest of the chemical community and culminated in two total syntheses of reveromycin B (**4**).[4,5] Related efforts, however, toward the synthesis of other members of this family of natural products have been less rewarding.[6]

SCHEME 1



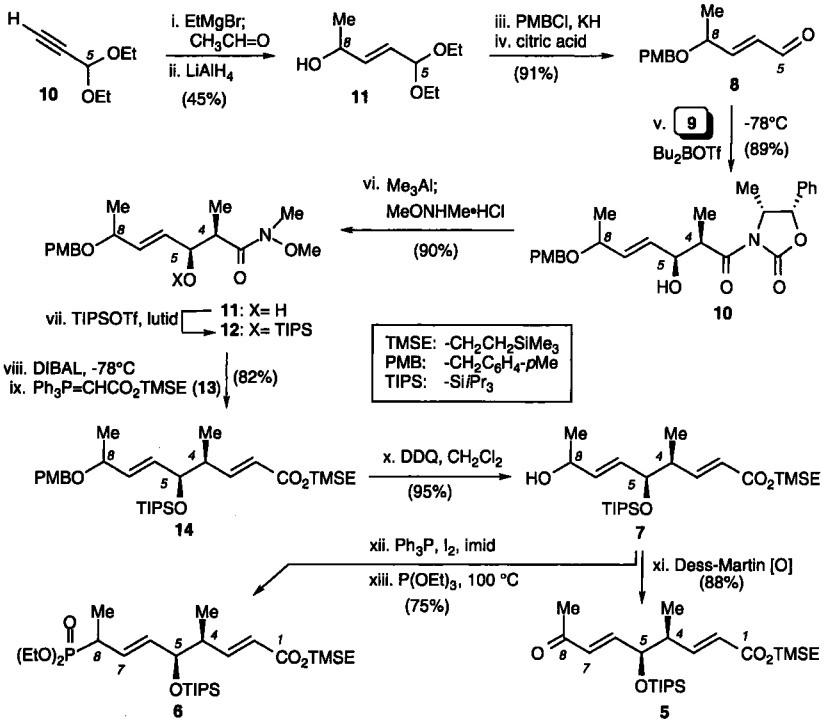
An attractive and potentially convergent synthetic approach toward this class of molecules may involve a disconnection across the C8-C9 double bond, which in the synthetic direction could be expected to occur by implementation of a Wittig-related olefination procedure. This approach led to the identification of ketone **5** or phosphonate **6**, which bear the desired stereochemistry at the C4 and C5 centers as

suitable synthetic targets. The desired fragments could be constructed from a common precursor **7**, in which the desired stereochemistry at the C4 and C5 centers could be introduced using Evans' asymmetric aldol methodology[7] (Scheme 1). Herein, we describe an efficient stereoselective synthesis of the C1-C8 fragment (right side chain) of these natural products.

Our synthetic approach departed with commercially available propargyl aldehyde dimethyl acetal (**10**) (Scheme 2). Addition of the magnesium salt of **10** to acetaldehyde, followed by $LiAlH_4$-mediated reduction of the resulting propargyl alcohol afforded allylic alcohol **11** in 45% overall yield.[8] Protection of the C8 hydroxyl group as the corresponding *p*-methoxybenzyl ether and subsequent exposure to mild acidic conditions (10% aqueous citric acid) furnished the corresponding aldehyde **8** (91% yield over two steps). Treatment of compound **8** with oxazolidinone **9**,[9] *n*-dibutylboron triflate and triethylamine at -78 °C gave rise to the desired syn aldol product **10** in 89% yield. Removal of the chiral auxiliary was achieved using the Weinreb conditions (Me_3Al, MeONHMe)[10] affording amide **11**, which was further transformed to silyl ether **12** upon treatment with TIPSOTf and lutidine (86% yield over two steps). Reduction of amide **12** with DIBAL-H afforded the corresponding aldehyde, which was immediately treated with ylide **13**[4] to produce the α,β unsaturated ester **7** exclusively as the *trans* isomer. Deprotection of the C8 PMB ether was accomplished with DDQ in wet dichloromethane and furnished allylic alcohol **7**, which was projected to be the versatile precursor of both fragments containing the C1-C8 side chain of reveromycins.

Indeed, conversion of **7** to ketone **5** was achieved in 88% yield, using Dess-Martin periodinane oxidation.[11] Alternatively, phosphonate ester **6** was obtained in 75% yield by treating **7** with triphenyl phosphine and iodine, followed by heating the newly formed iodide in excess triethylphosphite (Scheme 2).

SCHEME 2



Reagents and conditions: i. 1.0 equiv EtMgBr, THF, -10 °C, 2h; 2.0 equiv CH_3CHO, THF, -10 °C, 4h, 74%; ii. 1.5 equiv $LiAlH_4$, Et_2O, -25 °C, 6 h, 60%; iii. 1.2 equiv KH, 1.2 equiv PMBCl, Et_2O, 0 °C, 4 h; iv. 3.0 equiv citric acid (10% aqueous), THF, 25 °C, 2h, 91% (two steps); v. 1.0 equiv **9**, 1.2 equiv Et_3N, 1.1 equiv Bu_2BOTf (1.0 M in CH_2Cl_2), CH_2Cl_2, -78 to 0 °C, 2 h; 1.2 equiv **8**, CH_2Cl_2, -78 to 0 °C, 3h; 20 equiv NaOAc, MeOH, 10 equiv H_2O_2 (30% aqueous), 0 to 25 °C, 30 min, 89%; vi. 10 equiv MeONHMe•HCl, 2.1 equiv $AlMe_3$, THF, -30 °C, 5 min; 1.0 equiv **10**, THF, -10 to 0 °C, 3 h, 90%; vii. 1.5 equiv TIPSOTf, 3.0 equiv lutidine, CH_2Cl_2, 25 °C, 5 min, 95%; viii. 4.0 equiv DIBAL-H (1.5 M toluene), THF, -78 °C, 15 min; ix. 1.5 equiv Ph_3P=$CHCO_2TMSE$ (**13**), CH_2Cl_2, 25 °C, 30 min, 82% (two steps); x. 1.5 equiv DDQ, CH_2Cl_2/H_2O: 10/1, 25 °C, 15 min, 95%; xi. 1.5 equiv Dess-Martin, CH_2Cl_2, 25 °C, 15 min, 88%; xii. 2.4 equiv imidazole, 1.2 equiv Ph_3P, 1.2 equiv I_2, THF, 0 to 25 °C, 30 min; xiii. $P(OEt)_3$ (excess), 100 °C, 10h, 75% (two steps).

In summary, we presented a stereocontrolled synthesis of the C1-C8 fragment (right side chain) of reveromycins. The reported strategy is very efficient and delivers in a convergent manner two differently functionalized fragments, that could be employed toward the synthesis of reveromycins.

Selected experimental procedures/data: Organic solutions were concentrated by rotary evaporation below 45 °C at about 20 mmHg. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. NMR spectra were recorded on a Varian 500 MHz instrument and calibrated using residual undeuterated solvent as an internal reference. IR spectra were recorded on a Nicolet 320 Avatar FT-IR spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions.

Aldehyde 8. A solution of alcohol **11** (5.00 g, 28.7 mmol) in THF (250 ml) was cooled to 0 °C and treated with KH (1.38 g, 34.4 mmol) and 4-methoxybenzyl chloride (5.38 g, 34.4 mmol). After stirring for 6 h at 25 °C, the reaxtion mixture was cautiously poured onto ice (500 g), diluted with aqueous saturated NH_4Cl and extracted with ether (3 x 300 ml). The organic layer was collected, dried ($MgSO_4$), filtered and concentrated. The crude mixture was redissolved in THF (50 ml), treated with 10% solution of citric acid (50 ml), and stirred vigorously for 2 h. The mixture was diluted with water (150 ml) and extracted with ether (3 x 200 ml). The organic layer was washed with brine (150 ml), collected, dried ($MgSO_4$), filtered, concentrated and subjected to flash chromatography (silica, 0-10% ether in hexanes) to yield aldehyde **8** (5.75 g, 26.1 mmol, 91%). **8**: colorless liquid; R_f= 0.45 (silica, 20% ether in hexanes); IR (film) ν_{max} 2978, 2936, 2837, 1687, 1609, 1520, 1254, 1087, 825; ^1H NMR (500 MHz, $CDCl_3$) δ 9.60 (d, 1H, J= 5.0 Hz), 7.25 (d, 2H, J= 9.0 Hz), 6.89 (d, 2H,

J= 9.0 Hz), 6.77 (dd, 1H, J= 15.5, 10.0 Hz), 6.28 (dd, 1H, J= 16.0, 8.0 Hz), 4.49 (d, 1H, J= 11.0 Hz), 4.40 (d, 1H, J= 11.0 Hz), 4.25-4.20 (m, 1H), 3.80 (s, 3H), 1.34 (d, 3H, J= 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 159.3, 158.2, 131.5, 129.8, 129.2, 113.8, 73.3, 70.5, 55.1, 20.2; HRMS, calcd for $C_{13}H_{16}O_3$ ($M+Cs^+$) 353.0150, found 353.0178.

Oxazolidinone 10. A solution of oxazolidinone **9** (900 mg, 3.86 mmol) in CH_2Cl_2 (10 ml) was cooled to -78 °C and treated with Et_3N (480 µl, 4.74 mmol) and dibutylborontriflate (4.2 ml, 4.25 mmol, 1 M in CH_2Cl_2). The solution was stirred for 30 min at -78 °C, and then for 1 h at 0 °C. The mixture was cooled back to -78 °C, treated with aldehyde **9** (1.02 g, 4.63 mmol) in CH_2Cl_2 (5 ml), stirred at -78 °C for 30 min, and then warmed to 0 °C over a 2 h period. The resulting mixture was treated with NaOAc (3.0 g) in MeOH (50 ml) to which 30% H_2O_2 (4 ml) was added and stirred for 30 min from 0 to 25 °C. The reaction mixture was diluted with water (150 ml) and hexane (100 ml). The organic layer was separated, washed with brine (25 ml), dried ($MgSO_4$), concentrated, and submitted to flash chromatography (silica, 10-30% ether in hexanes) to afford oxazolidinone **10** (1.56, 3.43 mmol, 89% yield). **10**: sticky gum; R_f= 0.40 (silica, 33% ether in hexanes); $[\alpha]^{25}_D$: +6.70 (c= 2.2, CH_2Cl_2); IR (film) ν_{max} 3501, 2972, 2929, 1784, 1710, 1513, 1346, 1254, 1032; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.37 (m, 3H), 7.30-7.23 (m, 4H), 6.88 (d, 2H, J= 8.5 Hz), 5.79-5.60 (m, 3H), 4.77-4.74 (m, 1H), 4.55-4.47 (m, 2H), 4.33 (d, 1H, J= 10.5 Hz), 4.05-3.91 (m, 2H), 3.78 (s, 3H), 2.93-2.88 (m, 1H), 1.27 (d, 3H, J= 6.5 Hz), 1.25 (d, 3H, J= 7.0 Hz), 0.88 (d, 3H, J= 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 159.2, 152.8, 134.3, 133.2, 131.2, 130.9, 129.2, 128.8, 125.6, 113.8, 78.9, 74.8, 72.1, 69.7, 55.1, 46.1, 42.8, 21.4, 14.2, 11.2; HRMS, calcd for $C_{26}H_{31}NO_6$ ($M+Cs^+$) 586.1202, found 586.1231.

Amide 11. A suspension of N,O-dimethyl-hydroxylamine hydrochloride (2.15 g, 22.0 mmol) in THF (4 ml) was cooled to -30 °C and treated with $AlMe_3$ (11.0 ml, 5.50 mmol, 2.0 M in toluene) over a 3 min period. After the addition was complete, the solution was warmed to 25 °C and stirred for 15 min. The clear solution was cooled to -10 °C and treated with imide **95** (1.01 g, 2.20 mmol) in THF (10 ml, plus 5 ml rinse) added dropwise. The resulting mixture was warmed to 0 °C and stirred for 2.5 h. The reaction mixture was poured onto a rapidly stirring mixture containing aqueous saturated Rochelle's Salt (100 ml), saturated $NaHCO_3$ (50 ml) and ethyl acetate (150 ml) at 0 °C, and alllowed to warm to 25 °C. After 20 min, the resulting mixture was partitioned and the aqueous layer was extracted with ethyl acetate (2 x 150 ml). The organic layers were collected, dried ($MgSO_4$), filtered, concentrated, and subjected to flash chromatography (silica, 15-30% ether in hexanes) to yield amide **11** (667 mg, 1.94 mmol, 90%). **11**: sticky oil; R_f= 0.30 (silica, 65% ether in hexanes); $[a]^{25}_D$: -13.7 (c= 1.2, CH_2Cl_2); IR (film) ν_{max} 3446, 2978, 2935, 2867, 1642, 1513, 1242, 1039; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, 2H, J= 8.5 Hz), 6.87 (d, 2H, J= 8.5 Hz), 5.78 (dd, 1H, J= 15.5, 7.5 Hz), 5.66 (dd, 1H, J= 15.5, 5.0 Hz), 4.51 (m, 2H), 4.32 (d, 1H, J= 11.0 Hz), 3.78 (s, 3H), 3.70 (s, 3H), 3.19 (s, 3H), 3.19 (m, 1H), 2.96 (bs, 1H), 1.27 (d, 3H, J= 6.0 Hz), 1.18 (d, 3H, J= 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 133.7, 131.4, 130.9, 129.3, 113.8, 74.9, 71.7, 69.9, 61.6, 55.2, 39.4, 31.8, 21.5, 10.7; HRMS, calcd for $C_{18}H_{27}NO_5$ ($M+Cs^+$) 470.0940, found 470.0951.

Amide 12. A solution of the amide **11** (600 mg, 1.78 mmol) in CH_2Cl_2 (3 ml) at 25 °C was treated with 2,6-lutidine (625 µl, 5.36 mmol) and triisopropylsilyl trifluoromethanesulfonate (818 mg, 2.67 mmol). The mixture was stirred for 5 min, quenched with aqueous saturated $NaHCO_3$ (5 ml), diluted with

water (10 ml) and extracted with CH_2Cl_2 (3 x 20 ml). The organic layers were combined, dried ($MgSO_4$), filtered, concentrated and subjected to flash chromatography (silica, 0-15% ether in hexanes) to afford amide **12** (834 mg, 1.69 mmol, 95% yield). **12**: colorless oil. R_f= 0.45 (silica, 33% ether in hexanes); $[a]^{25}_D$: +7.78 (c= 1.4, CH_2Cl_2); IR (film) ν_{max} 2941, 2868, 1661, 1515, 1457, 1249, 1060, 878; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, 2H, J=8.5 Hz), 6.86 (d, 2H, J= 8.5 Hz), 5.75 (dd, 1H, J= 15.5, 7.5 Hz), 5.58 (dd, 1H, J= 15.5, 7.5 Hz), 4.49 (d, 1H, J= 11.5 Hz), 4.42-4.37 (m, 1H), 4.27 (d, 1H, J= 11.5 Hz), 3.89-3.87 (m, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 3.11 (m, 1H), 3.11 (s, 3H), 1.24-1.19 (m, 6H), 1.07-1.05 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 133.8, 133.6, 131.0, 129.3, 113.7, 75.7, 74.9, 69.6, 61.4, 55.1, 42.9, 30.8, 21.6, 18.04, 18.01, 14.5, 12.5; HRMS, calcd for $C_{27}H_{47}NO_5Si$ ($M+Cs^+$) 626.2274, found 626.2281.

Ester 14. A solution of amide **12** (800 mg, 1.62 mmol) in THF (5 ml) was cooled to -78 °C and treated with DIBAL-H (4.3 ml, 6.48 mmol, 1.5 M in toluene). After 15 min, the reaction mixture was quenched with MeOH (2 ml), diluted with ethyl acetate (20 ml), Rochelle's salt (20 ml) and stirred for 30 min at 25 °C. The mixture was partitioned and the aqueous layer was extracted with ethyl acetate (3 x 20 ml). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. The crude aldehyde was dissolved in CH_2Cl_2 (3 ml) and treated with ylide **13** (1.02 g, 2.43 mmol) at 25 °C for 15 h. The resultant mixture was concentrated and subjected to flash chromatography (silica, 0-10% ether in hexanes) to afford ester **14** (761 mg, 1.33 mmol, 82% yield). **14**: colorless oil; R_f = 0.35 (silica, 12% ether in hexanes); $[\alpha]^{25}_D$: -5.20 (c= 1.1, CH_2Cl_2); IR (film) ν_{max} 2946, 2868, 1719, 1515, 1249, 1170, 1040, 836; ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, 2H, J= 8.5 Hz), 7.10 (dd, 1H, J= 16.5, 6.5 Hz), 6.87 (d, 2H,

J=8.5 Hz), 5.82 (m, 1H), 5.59 (m, 2H), 4.46 (d, 1H, J=11.5 Hz), 4.26-4.17 (m, 4H), 3.94-3.82 (m, 1H), 3.79 (s, 3H), 2.60-2.54 (m, 1H), 1.23 (d, 3H, J= 6.5 Hz), 1.09-0.95 (m, 26H), 0.020 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 159.1, 150.5, 134.3, 132.7, 130.9, 129.2, 121.6, 113.8, 76.7, 74.9, 69.6, 62.3, 55.2, 43.4, 21.9, 18.0, 17.96, 17.1, 14.8, 12.3, -1.6; HRMS, calcd for $C_{32}H_{56}O_5Si_2$ ($M+Cs^+$) 709.2717, found 709.2729.

Alcohol 7. A solution of ester **14** (500 mg, 0.867 mmol) in CH_2Cl_2 (2 ml) containing H_2O (200 μl) was treated with 2,3-dichloro,5,6-dicyano benzoquinone (295 mg, 1.30 mmol) at 25 °C for 15 min. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ (10 ml), filtered through a short pad of celite, diluted with CH_2Cl_2 (40 ml) and extracted with water (2 x 15 ml). The organic layer was dried ($MgSO_4$), concentrated and subjected to flash chromatography (silica, 10-25% ether in hexanes) to produce alcohol **7** (376 mg, 0.824 mmol, 95% yield). **7**: colorless oil; R_f= 0.25 (33% ether in hexanes); $[\alpha]^{25}_D$: -3.35 (c= 1.22, CH_2Cl_2); IR (film) ν_{max} 3434, 2960, 2867, 1734, 1648, 1463, 1254, 1057, 842; ^1H NMR (500 MHz, $CDCl_3$) δ 7.05 (dd, 1H, J= 16.0, 7.5 Hz), 5.77 (dd, 1H, J= 15.5, 4.5 Hz), 5.65 (dd, 1H, J= 15.5, 5.0 Hz), 5.56 (dd, 1H, J= 15.5, 6.5 Hz), 4.29 (t, 1H, J= 6.5 Hz), 4.22-4.15 (m, 3H), 2.53-2.51 (m, 1H), 1.66 (bs, 1H), 1.23 (d, 3H, J= 6.0 Hz), 1.03-0.98 (m, 26H), 0.92 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 150.6, 136.2, 130.3, 121.5, 76.6, 68.2, 62.3, 43.3, 23.2, 18.0, 17.9, 17.2, 14.5, 12.3, -1.6; HRMS, calcd for $C_{24}H_{48}O_4Si_2$ ($M+Cs^+$) 589.2142, found 589.2169.

Ketone 5. A solution of the alcohol **7** (100 mg, 0.219 mmol) in CH_2Cl_2 (3 ml) was treated with Dess-Martin periodinane (140 mg, 0.328 mmol) at 25 °C. After 15 min, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (5 ml) and $Na_2S_2O_8$, diluted with ether (10 ml) and the layers were

separated. The aqueous layer was extracted with ether (2 x 15 ml) and the organic layers were combined, dried ($MgSO_4$), filtered, concentrated, and subjected to flash chromatography (silica, 0-10% ether in hexanes) to yield ketone **5** (87 mg, .193 mmol, 88%). **5**: light yellow oil; R_f= 0.35 (12% ether in hexanes); $[\alpha]^{25}_D$: -6.17 (c= 1.07, CH_2Cl_2); IR (film) ν_{max} 2957, 2868, 1719, 1677, 1254, 1175, 836; ^1H NMR (500 MHz, $CDCl_3$) δ 7.01 (dd, 1H, J= 16.0, 8.5 Hz), 6.65 (dd, 1H, J= 16.0, 10.0 Hz), 6.18 (d, 1H, J= 16.5 Hz), 5.80 (d, 1H, J= 16.0 Hz), 4.40-4.38 (m, 1H), 4.22 (t, 2H, J= 8.0 Hz), 2.66-2.63 (m, 1H), 2.24 (s, 3H), 1.07-0.99 (m, 26H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 166.6, 149.1, 146.5, 131.1, 122.3, 75.7, 62.4, 43.1, 27.2, 17.93, 17.92, 17.1, 14.4, 12.3, -1.6; HRMS, calcd for $C_{24}H_{46}O_4Si_2$ ($M+Cs^+$) 587.1986, found 587.1992.

Phosphonate 6. A solution of the alcohol **7** (100 mg, 0.219 mmol) in THF (3 ml) at 25 °C was treated with imidazole (36 mg, 0.526 mmol), and triphenylphosphine (69 mg, 0.263 mmol). After 5 min the mixture was cooled to 0 °C, covered with alumina foil and treated with iodine (67 mg, 0.263 mmol). The reaction was warmed to 25 °C and stirred for 10 min. The solution was quenched with $Na_2S_2O_8$ (5 ml) and diluted with ether (10 ml). The aqueous layer was extracted with ether (3 x 10 ml), dried ($MgSO_4$), filtered, concentrated in the dark, and subjected to flash chromatography (silica, 0-5% ether in hexanes). The unstable iodide was immediately treated with triethylphosphite (3 ml) and heated in a sealed tube at 100 °C in the dark. After 10 hr, the reaction mixture was concentrated under reduced pressure (60 °C, 0.3 mm Hg), and subjected to flash chromatography (silica, 0-25% ether in hexanes) to afford phosphonate **6** (90 mg, 0.164 mmol, 75% yield). **6**: light yellow oil; R_f= 0.25 (50% ether in hexanes); $[\alpha]^{25}_D$: -6.17 (c= 1.07, CH_2Cl_2); IR (film) ν_{max} 2946, 2863, 1719, 1463, 1254, 1175, 836; ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (dd, 1H, J= 16.0, 8.5 Hz), 5.78

(dd, 1H, J= 16.0, 10.0 Hz), 5.67 (m, 1H), 5.53 (m, 1H), 4.21 (t, 3H, J= 8.5 Hz), 4.10-4.06 (m, 4 H), 2.66-2.48 (m, 2H), 1.30-1.23 (m, 12 H), 1.06-0.99 (m, 23H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 166.6, 149.1, 146.5, 131.1, 122.3, 75.7, 62.4, 43.1, 27.2, 17.93, 17.92, 17.1, 14.4, 12.3, -1.6; HRMS, calcd for $C_{28}H_{57}O_6PSi_2$ ($M+Cs^+$) 609.2482, found 609.2485

Acknowledgment: This work was supported by the Cancer Research Coordinating Committee, the American Cancer Society (RPG CDD-9922901) and the Hellman Foundation.

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Received in the USA 1/15/00