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DESIGN AND SYNTHESIS OF 16-MEMBERED HYBRID MACROLIDE HAVING A THIAZOLE SIDE CHAIN ON THE CARBONOLIDE SKELETON

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Abstract – Design and synthesis of a 16-membered hybrid macrolide, which contained a 16-membered carbonolide-type lactone framework with a thiazole sidechain, were described.

INTRODUCTION

A number of new classes of macrolide with a variety of characteristics involving not only the structure but also the biological activity have been discovered.[1] Epothilones, isolated from the mycobacterium *Sorangenium cellulosum* in 1996, are a new class of 16-membered macrolides showing a taxiol-like activity.[2,3] Due to its significant biological activity and unique structure, considerable synthetic efforts have been devoted to the total synthesis of epothilone and its analogs.[4] We reported the total synthesis of a typical 16-membered macrolide aglycon by taking advantage of the benzyl-type protecting groups and intramolecular Wittig-Horner macrolactonization method.[5,6] In this paper we describe a design and synthesis of a 16-membered hybrid macrolide (**1**) having a thiazole sidechain on the carbonolide-type 16-membered lactone skeleton, which was readily synthesized from ketophosphonate carboxylic acid (**2**) and aldehyde alcohol (**3**) by Yamaguchi esterification[7] followed by Horner-Emmons reaction.

RESULTS AND DISCUSSION

Synthesis of the C1-C10 fragment[9]

The C1-C10 fragment (**2**) was prepared by a 4-step sequences starting from reported tylonolide synthon[5] (**4**) (Scheme 1). The 3,4-dimethoxybenzyl (DMPM) protecting group at the C6'' hydroxy group was exchanged into a *tert*-butyldiphenylsilyl (TBDPS) group in 72 % yield. The masking double bond was cleaved to the carboxylic acid. Dihydroxylation of **6** with OsO_4-NMO, followed by $NaIO_4$ oxidation gave

This paper is dedicated to Dr. Pierre Potier on the occasion of his 70th birthday.

an aldehyde (**7**), which was oxidized with $NaClO_2$ to give a carboxylic acid (**2**) in 62 % yield from **4** (4 steps).

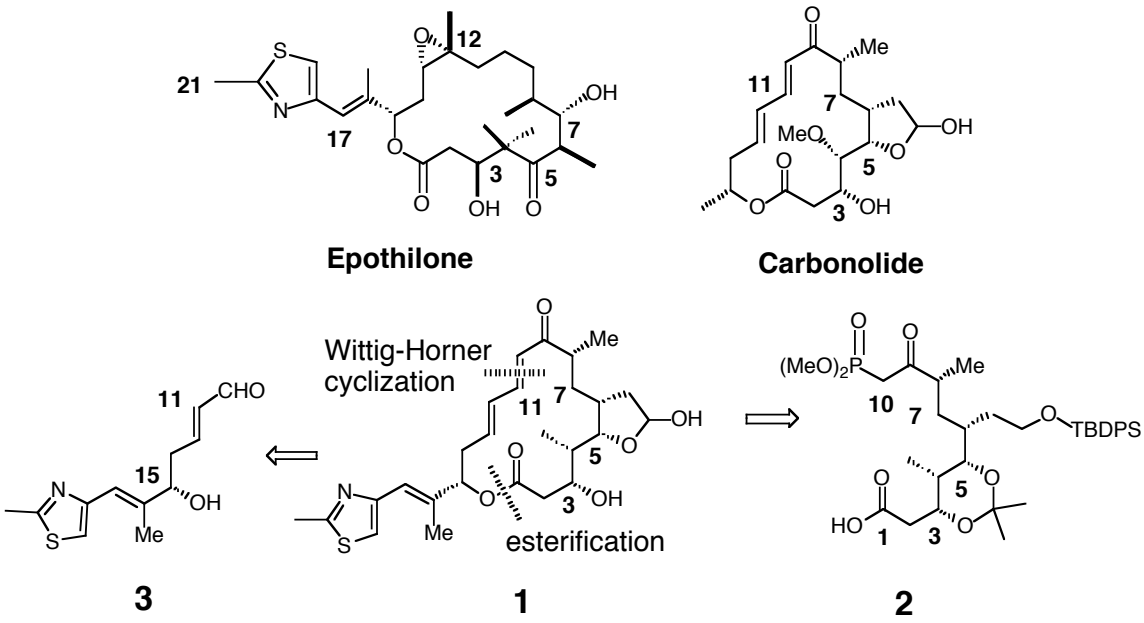
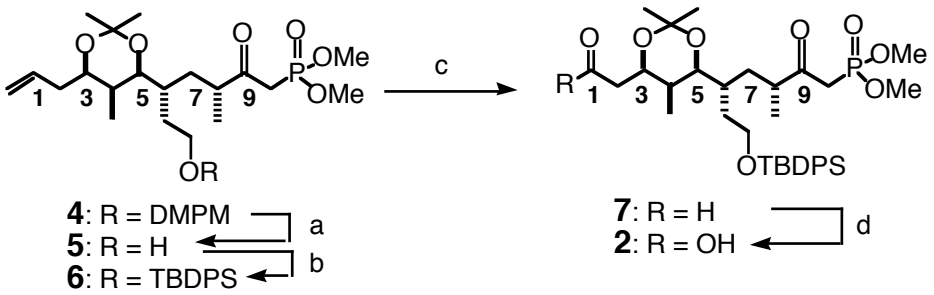


Figure 1



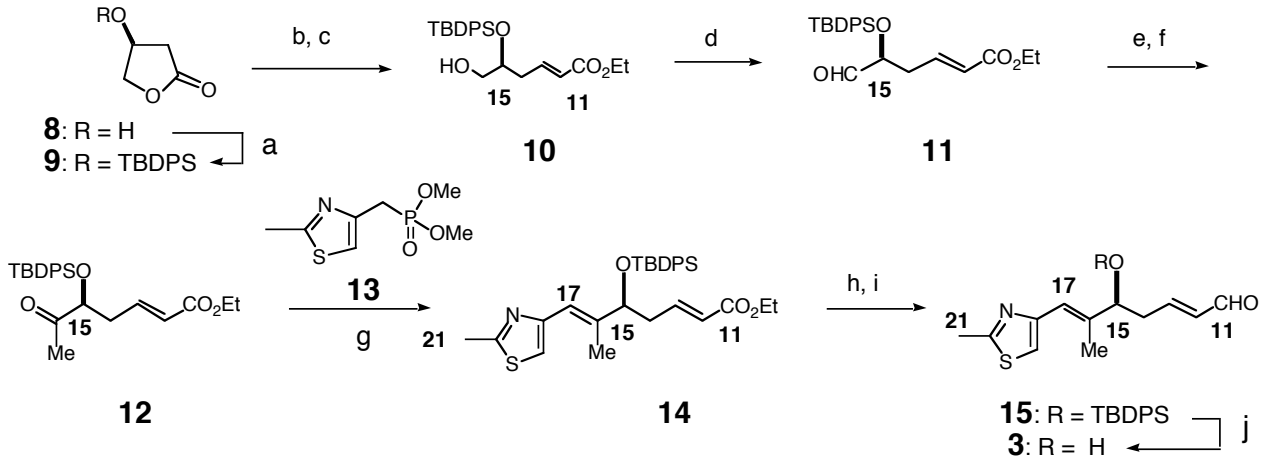
reagent and conditions: a) DDQ, CH_2Cl_2/H_2O, 80 % b) TBDPSCl, imidazole, CH_2Cl_2, 90 % c) OsO_4, NMO, *t*-BuOH/H_2O and then $NaIO_4$, *t*-BuOH/H_2O, 83 % d) $NaClO_2$, NaH_2PO_4, *t*-BuOH/H_2O, 2-methyl-2-butene, 100 %

Scheme 1

Synthesis of the C11-C21 fragment

Synthesis of C11-C21 fragment (**3**) was achieved starting from (*S*)-(-)-β-hydroxy-γ-butyrolactone (**8**) as shown in **Scheme 2**. The hydroxyl group of **8** was protected with a TBDPS group and following DIBAL reduction and (carbethoxymethylene)triphenylphosphorane treatment provided an *E*/*Z* mixture of α,β-unsaturated ester (**10**) with 4.3/1 ratio in 96% yield. After removal of the *Z*–α,β-unsaturated ester by column chromatography, the primary alcohol was oxidized to aldehyde under Swern conditions. Methylmagnesium bromide addition followed by Swern oxidation afforded methyl ketone (**12**) in 39% yield (2 steps). The thiazole functionality (**13**) was connected with **12** by Horner-Wadsworth-Emmons olefination to give the trisubstituted olefin (**14**) as a single *E*-geometry in 50 % yield. Ethyl ester was converted into aldehyde (**15**) in a 2-step procedure; DIBAL reduction and Dess-Martin periodinane oxidation. Finally, the TBDPS group was removed with TBAF[10] in the presence of AcOH to afford the

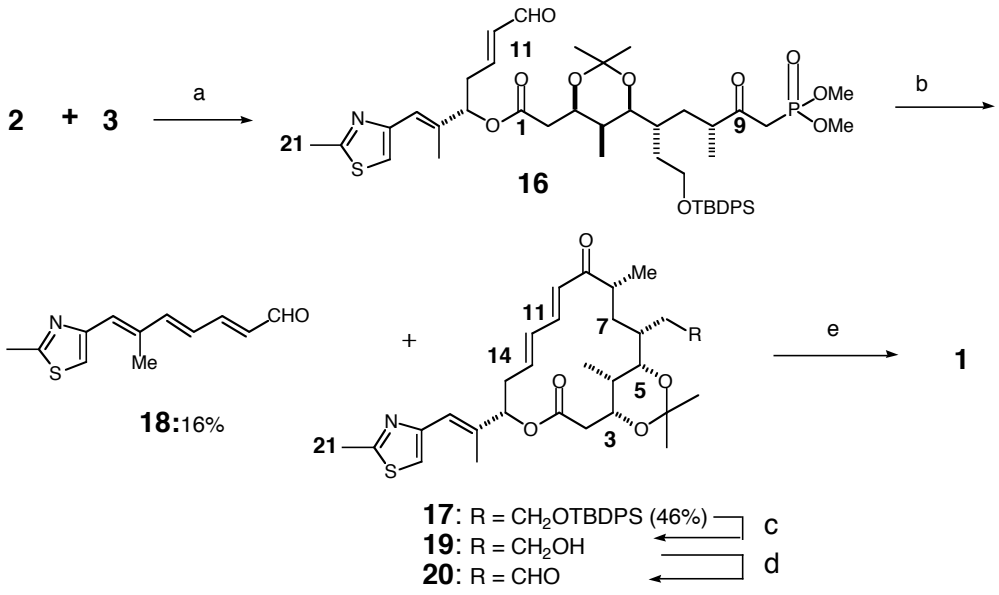
C11-C21 fragment (**3**) in 75 % (10 steps, total yield 10 %).



reagent and conditions: a) TBDPSCl, Imidazole, CH_2Cl_2, 97 % b) DIBAL, CH_2Cl_2, c) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 78 % (2 steps) d) $(COCl)_2$-DMSO, TEA, CH_2Cl_2, -78°C, 100 % e) MeMgBr, Et_2O/hexane, 44 % f) $(COCl)_2$-DMSO, TEA, CH_2Cl_2, -78°C, 88 % g) BuLi/THF, 28 % h) DIBAL, CH_2Cl_2, -78°C i) Dess-Martin oxi. , CH_2Cl_2, 96 % (2 steps) j) TBAF, AcOH, THF, 60 %

Scheme 2

The two fragments, C1-C10 fragment (**2**) and the C11-C21 fragment (**3**), were coupled into the ester (**16**) in 76% yield by the Yamaguchi method using 2,4,6-trichlorobenzoyl chloride and 4-dimethylaminopyridine (DMAP) in toluene (**Scheme 3**). The obtained **16** was next subjected to macrocyclization, which is usually the most crucial step in the synthesis of macrolides. Macrocyclization of **16** into **17** was accomplished by an intramolecular Horner-Emmons reaction. When a 1 mM solution of **16** in toluene was treated with K_2CO_3 (6 equiv.) and 18-crown-6 (12 equiv.)[11] at rt for 23 h, the



reagents and conditions: a) 2,4,6-C_2H_6COCl, NEt_3 DMAP, toluene, rt, 76% b) K_2CO_3, 18-crown-6, toluene, rt, 1mM solution c) TBAF, Ac_2O/THF, 96% d) Dess-Martin oxi./CH_2Cl_2, 63 % e) 1N HCl/THF, 65 %

Scheme 3

cyclization slowly proceeded to give the expected 16-membered lactone (**17**) in 46% yield with the concomitant formation of conjugate aldehyde (**18**) in 16 % yield. 16-Membered lactone (**17**) was converted to hemiacetal (**1**). The TBDPS group of the 6'' hydroxy group was deprotected by TBAF treatment in 86 % yield and the resulting alcohol was oxidized to aldehyde (**20**) by Dess-Martin periodinane in 63 % yield. Acid hydrolysis of the acetonide of **20** with 1N HCl-THF (1/3) gave the hemiacetal (**1**) in 65 % yield as a 3/1 mixture of anomers.

Antibacterial activity for *Staphylococcus aureus, Micrococcus luteus* ATCC9341, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* was assayed for 1, which did not show any activity at 32μg/mL (MIC).

EXPERIMENTAL

All melting points were measured with Yamato melting point apparatus model MP-21 and are uncorrected. Optical rotations were measured with a JASCO DIP-4 digital polarimeter and HORIBA high-sensitive polarimeter SEPA-300. IR spectra were recorded in $CHCl_3$ or neat on a JASCO IRA-2 spectrometer and a SHIMADZU OR-8000 spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a JEOL JNM GX-270, JEOL JNM EX-400, and JEOL JNM LA-400 instrument. Low- and high-resolution mass spectra (MS) were taken on a JEOL JMS HX-110, JEOL JMS DX-303 and JEOL JMS AX-500 spectrometer.

Dimethyl (3*R*, 5*R*, 6*S*, 7*S*, 8*R*)-5-(2-Hydroxyethyl)-6,8-isopropylidenedioxy-3, 7-dimethyl-2-oxo-10-undecenylphosphonate (5): DDQ (60.0 mg, 0.175 mmol) was added to a stirred solution of **4** (100 mg, 0.175 mmol) in CH_2Cl_2 (3 mL) and H_2O (0.15 mL). After being stirred for 1 h, the reaction mixture was quenched by adding of sat. aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with EtOAc (10 mL x 3), and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (CH_2Cl_2/MeOH, 30/1) to give **5** (59.2 mg, 80 %) as a colorless oil: Rf = 0.15 (CH_2Cl_2/MeOH = 30/1); ^{1}H-NMR (400 MHz, $CDCl_3$) 5.75 (1H, dddd, *J* = 6.1, 7.8, 10.0, 16.9 Hz), 5.21 (1H, dq, *J* = 16.9, 1.7 Hz), 5.07 (1H, dd, *J* = 1.0, 10.0 Hz), 3.86 (1H, dt, *J* = 2.0, 7.0 Hz), 3.83-3.75 (1H, m), 3.79 (3H, d, *J* = 11.2 Hz), 3.77 (3H, d, *J* = 11.2 Hz), 3.63-3.70 (1H, m), 3.58 (1H, dd, *J* = 2.0, 9.5 Hz), 3.17 (2H, d, *J* = 22.2 Hz), 2.92-3.0 (1H, m), 2.30 (1H, dddd, *J* = 1.7, 6.1, 7.1, 13.9 Hz), 2.30-2.22 (1H, m), 2.13 (1H, ddd, *J* = 7.1, 7.8, 13.9 Hz), 1.93 (1H, ddd, *J* = 5.1, 6.8, 14.1 Hz), 1.75-1.68 (1H, m), 1.61 (1H, ddd, *J* = 3.4, 7.3, 14.4 Hz), 1.53 (1H, dt, *J* = 2.0, 6.8 Hz), 1.41 (3H, s), 1.39 (3H, s), 1.27 (1H, ddd, *J* = 3.3, 5.3, 14.4 Hz), 1.19 (1H, dt, *J* = 5.7, 14.4 Hz), 1.10 (3H, d, *J* = 6.8 Hz), 0.86 (3H, d, *J* = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 205.9, 134.3, 16.9, 98.8, 77.4, 73.1, 59.8, 53.1 (d, *J* = 6.6 Hz), 52.7 (d, *J* = 6.6 Hz), 46.4, 39.0 (d, *J* = 132.1 Hz), 37.1, 34.6, 34.1, 32.7, 32.3, 29.8, 19.5, 16.5, 4.6; IR (neat, cm^{-1}) 3440 (m), 2940 (m), 1717 (s), 1458 (m), 1390 (m), 1380 (m), 1260 (s), 1200 (s), 1175 (m), 1036 (s), 916 (m), 733 (s); FAB-MS (m/z) 422 (3.4), 421 ($[M+H]^+$, 11), 363 (11), 345 (41), 263 (83), 193 (80), 165 (69), 151 (100); FAB-HRMS calcd for $C_{20}H_{38}O_7P$ $[M+H]^+$, 421.2355; found 421.2343.

Dimethyl (3*R*,5*R*,6*S*,7*S*,8*R*)-5-{2-(*tert*-Butyldiphenylsilyloxy)ethyl}-6,8-isopropylidenedioxy-3,7-dimethyl-2-oxo-10-undecenylphosphonate (6): A CH_2Cl_2 solution (3.0 mL) of *tert*-butyldiphenylchlorosilane (53 μL, 0.20 mmol), **5** (57.0 mg, 0.40 mmol) and imidazole (27.2 mg, 0.40 mmol) was stirred at rt for 0.5 h. The reaction mixture was diluted with EtOAc (10 mL) and the whole was washed with sat. aquous NH_4Cl solution. The separated aqueous layer was further extracted with EtOAc (10 mL x 2). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 1/1 to 1/2) to give a **5** (80.9 mg, 90 %) as a colorless oil: Rf = 0.25 (hexane/EtOAc = 1/1); $[\alpha]_D^{27}$ = -2.0° (*c* 0.7, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) 7.66-7.64 (4H, m), 7.45-7.36 (6H, m), 5.75 (1H, dddd, *J* = 6.1, 7.8, 10.0, 17.3 Hz), 5.11 (1H, dd, *J* = 1.7, 17.3 Hz), 5.06 (1H, d, *J* = 10.0 Hz), 3.82 (1H, dt, *J* = 1.7, 7.1 Hz), 3.762 (3H, d, *J* = 11.2 Hz), 3.758 (3H, d, *J* = 11.2 Hz), 3.65 (2H, dd, *J* = 5.6, 7.3 Hz), 3.59 (1H, dd, *J* = 1.7, 9.5 Hz), 3.12 (2H, d, *J* = 22.4 Hz), 2.90-2.83 (1H, m), 2.28 (1H, dddd, *J* = 1.7, 6.1, 7.1, 13.9 Hz), 2.11 (1H, ddd, *J* = 7.1, 7.8, 13.9 Hz), 1.76-1.58 (2H, m), 1.63-1.55 (1H, m), 1.46 (1H, tq, *J* = 1.7, 6.8 Hz), 1.39 (6H, s), 1.25-1.17 (1H, m), 1.13-1.08 (1H, m), 1.04 (9H, s), 1.03 (3H, d, *J* = 7.0 Hz), 0.82 (3H, d, *J* = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 205.9, 135.6, 135.5, 134.6, 133.6, 129.70 129.67, 127.7, 127.7, 116.8, 98.8, 78.1, 73.1, 60.8, 52.9 (d, *J* = 5.8 Hz), 52.8 (d, *J* = 5.8 Hz), 47.1, 38.9 (d, *J* = 132 Hz), 37.3, 34.7, 33.9, 32.4, 32.3, 29.9, 26.9, 19.6, 19.1, 15.7, 4.6; IR (neat, cm^{-1}) 3073 (w), 2934 8s9, 2857 (m), 1715 (s), 1462 (m), 1429 (m), 1386 (m), 1380 (m), 1262 (s), 1200 (s), 1175 (m), 1111 (s), 1034 (s), 1013 (s), 704 (s); FAB-MS (m/z) 683 (19), 682 (45), 681 ($[M+Na]^+$, 100), 601 (11); FAB-HRMS calcd for $C_{36}H_{55}O_7NaPSi$ $[M+Na]^+$, 681.3352; found 681.3317.

(3*R*,4*S*,5*S*,6*R*,8*R*)-10-Dimethoxyphosphono-6-{2-(*tert*-butyldiphenylsilyloxy)ethyl}-3,5-isopropylidenedioxy-3,8-dimethyl-9-oxodecanal (7): A solution of **6** (77.2 mg, 0.12 mmol) and NMO (47.4 mg, 0.36 mmol) in acetone (3 mL) and H_2O (1 mL) were added to a 2.5% t-BuOH solution of OsO_4 (60 μL, 0.006 mmol) at rt. After stirring at rt for 21 h, aqueous solution of $NaIO_4$ (440 mg in 2.9 mL H_2O) was added to the reaction mixture and stirring was continued for 30 min. The reaction mixture was filtered, then the filtrate was extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were washed with sat. aqueous NH_4Cl solution, dried (Na_2SO_4), then filtered. The residue was purified by silica gel column chromatography (hexane/EtOAc, 1/1 to 1/2) to afford **7** (64.1 mg, 83 %) as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) 9.74 (1H, dd, *J* = 1.7, 2.2 Hz), 7.66-7.63 (4H, m), 7.45-7.36 (6H, m), 4.37 (1H, ddd, *J* = 2.5, 3.6, 9.0 Hz), 3.765 (3H, d, *J* = 11.2 Hz), 3.761 (3H, d, *J* = 11.2 Hz), 3.66 (2H, t, *J* = 7.3 Hz), 3.65 (1H, dd, *J* = 2.5, 7.3 Hz), 3.11 (2H, d, *J* = 22.2 Hz), 3.40-3.32 (1H, m), 2.65 (1H, ddd, *J* = 2.2, 9.1, 16.6 Hz), 2.28 (1H, ddd, *J* = 1.7, 3.9, 16.6 Hz), 1.77-1.68 (2H, m), 1.59 (1H, ddt, *J* = 2.5, 12.4, 7.3 Hz), 1.44 (1H, tq, *J* = 2.5, 6.8 Hz), 1.42 (3H, s), 1.37 (3H, s), 1.25-1.18 (1H, m), 1.11 (1H, ddd, *J* = 3.5, 8.3, 13.5 Hz), 1.04 (9H, s), 1.035 (3H, d, *J* = 6.8 Hz), 0.83 (3H, d, *J* = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 206.7 (d, *J* = 6.6 Hz), 201.0, 135.5, 129.67, 129.64, 99.1, 77.7, 68.5, 60.6, 52.9 (d, *J* = 5.7 Hz), 52.8 (d, *J* = 5.7 Hz), 46.9, 38.9 (d, *J* = 134.1 Hz), 34.5, 33.8, 32.9, 32.1, 29.7, 26.8, 19.5, 19.0, 15.8, 14.1, 5.1; FAB-MS (m/z) 685 (9), 684 (25), 683 ($[M+Na]^+$, 53), 603 (100); FAB-HRMS calcd for $C_{35}H_{53}O_8NaPSi$ $[M+Na]^+$, 683.3145; found, 683.3170.

(*S*)-(-)-β-*tert*-Butyldiphenylsilyloxy-g-butyrolactone (9): To a stirred solution of (*S*)-(-)-β-hydroxy-γ-butyrolactone (**8**, 1.02 g, 10 mmol) and imidazole (1.50 g, 22 mmol) in CH_2Cl_2 (20 mL) was added a solution of *tert*-butyldiphenylchlorosilane (2.86 mL, 11 mmol) in CH_2Cl_2 (10 mL) under nitrogen atmosphere at rt. After stirring at rt for 30 min, the precipitated inorganic salt was filtered off and the filtrate was washed with sat. aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 5/1) to afford **9** (3.28 g, 97 %) as a colorless solid: mp 119.5-120.5°C (EtOAc/hexane); $[\alpha]_D^{27}$ = -7.9° (*c* 1.05, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) 7.66-7.61 (4H, m), 7.48-7.39 (6H, m), 4.55 (1H, dddd, *J* = 2.6, 3.7, 4.6, 5.1 Hz), 4.19 (1H, dd, *J* = 2.6, 9.8 Hz), 4.15 (1H, dd, *J* = 4.6, 9.8 Hz), 2.51 (1H, dd, *J* = 5.1, 17.8 Hz), 2.47 (1H, dd, *J* = 3.7, 17.8 Hz), 1.06 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) 175.6, 135.5, 132.7, 130.2, 128.0, 75.6, 69.0, 37.8, 26.7, 18.9; IR (KBr, cm^{-1}) 2932 (w), 2959 (w), 1786 (s), 1428 (m), 1165 (m), 1115 (s), 1105 (s), 1092 (s), 1013 (m), 997 (m), 822 (m), 702 (s); FAB-MS (m/z) 365 (8), 364 (29), 363 ($[M+Na]^+$, 100), 342 (12), 341 ($[M+H]^+$, 42), 283 (44), 263 (29), 241 (73), 221 (76), 199 (37), 137(94); FAB-HRMS calcd for $C_{20}H_{25}O_3Si$ $[M+H]^+$, 341.1573; found 341.1562.

Ethyl (2*E*)(5*S*)-5-*tert*-Butyldiphenylsilyloxy-6-hydroxyhex-2-enoate (10): To a stirred solution of **9** (2.93 g, 8.6 mmol) in CH_2Cl_2 (20 mL) was successively added a solution of 1 M CH_2Cl_2 solution of DIBAL (9 mL, 9 mmol) at –78°C. After stirring at rt for 30 min, the reaction was quenched with sat. aqueous NH_4Cl solution (20 mL), and the mixture was extracted with CH_2Cl_2 (25 mL x 3). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo* to give the hemiacetal as a colorless oil, which was used in the next reaction without further purification.
A stirred solution of hemiacetal (2.93 g, 8.6 mmol) and (carbethoxymethylene)triphenylphosphorane (3.0 g, 8.6 mmol) in CH_2Cl_2 (40 mL) was stirred at rt for 12 h. The precipitated salt was filtered off and the filtrate was evaporated *in vacuo* to leave an oil, which was purified by silica gel column chromatography (hexane/EtOAc, 8/1 to 3/1) to afford *cis*-**10** (0.63 g, 18 %) as a colorless oil from the first fraction and *trans*-**10** (2.76 g, 78 %) as a colorless oil from the second fraction: ^{1}H-NMR (400 MHz, $CDCl_3$) 7.69-7.65 (4H, m), 7.47-7.38 (6H, m), 6.80 (1H, ddd, *J* = 7.3, 7.6, 15.6 Hz), 5.73 (dt, *J* = 15.6, 1.5 Hz), 4.16 (2H, q, *J* = 7.1 Hz), 3.89 (1H, dddd, *J* = 4.2, 4.6, 5.4, 7.3 Hz), 3.53 (1H, ddd, *J* = 4.2, 5.9, 11.5 Hz), 3.47 (1H, ddd, J = 4.6, 7.0, 11.5 Hz), 2.43 (1H, ddt, J = 1.5, 14.4, 7.6 Hz), 2.33 (1H, dddd, J = 1.5, 5.4, 7.3, 14.4 Hz), 1.72 (1H, dd, J = 5.9, 7.0, OH), 1.28 (3H, t, J = 7.1 Hz), 1.07 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) 166.2, 144.3, 135.9, 135.7, 133.6, 133.3, 130.0, 127.9, 127.8, 123.9, 72.8, 65.6, 60.2, 36.5, 27.0, 19.3, 14.2; IR (neat, cm^{-1}) 3600-3200 (m), 2959 (s), 2934 (s), 2859 (s), 1720 (s), 1705 (s), 1655 (m), 1590 (s), 1474 (m), 1428 (s), 1370 (m), 1320 (m), 1269 (s), 1171 (s), 1111 (s), 1046 (s), 988 (m), 822 (m), 741 (m), 704 (m); FAB-MS (m/z) 437 (2), 436 (7), 435 ($[M+Na]^+$, 21), 413 ($[M+H]^+$, 2), 367 (11), 335 (27), 277 (30), 257 (38), 241 (25), 221 (60), 199 (75), 135 (100); FAB-HRMS calcd for $C_{24}H_{32}O_4NaSi$ $[M+Na]^+$, 435.1968; found 435.1939.

Ethyl (2*E*)(5*S*)-5-*tert*-Butyldiphenylsilyloxy-6-oxohex-2-enoate (11): A solution of DMSO (329 μL,

4.63 mmol) in dry CH_2Cl_2 (10 mL) was added to a stirred solution of oxalyl chloride (232 μL, 2.32 mmol) in dry CH_2Cl_2 (1 mL) at -78°C. After 15 min, a CH_2Cl_2 (3 mL) solution of **10** (478 mg, 1.16 mmol) was added to the reaction mixture. Stirring was continued for 15 min at -78°C, and then Et_3N (969 mL, 6.95 mmol) was added. After 30 min at -78°C, the reaction mixture was quenched with sat. aqueous NH_4Cl solution. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 5 /1) to afford **11** (476 mg, 100%) as a colorless oil: Rf = 0.33 (hexane/EtOAc, 7/1); ^{1}H-NMR (100 MHz, $CDCl_3$) 9.60 (1H, d, *J* = 1.2 Hz), 7.65-7.63 (4H, m), 7.45-7.37 (6H, m), 6.86 (1H, dt, *J* = 15.6, 7.5 Hz), 5.82 (1H, dt, *J* = 15.6, 1.5 Hz), 4.18 (2H, q, *J* = 7.0 Hz), 4.13 (1H, dt, *J* = 1.2, 5.6 Hz), 2.27-2.21 (2H, m), 1.28 (1H, t, *J* = 7.0 Hz), 1.12 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) 202.7, 165.9, 42.5, 135.8, 132.6, 130.2, 127.9, 124.9, 76.8, 60.3, 35.7, 26.9, 19.3, 14.2; IR (neat, cm^{-1}) 2934 (m), 2859 (m), 1739 (s), 1721 (s), 1655 (m), 1474 (m), 1428 (m), 1368 (m), 1267 (m), 1175 (m), 1113 (s), 1044 (m), 986 (m), 822 (m), 741 (m), 702 (s); FAB-MS (m/z) 435 (1), 434 (4), 433 ($[M+Na]^+$, 12), 411 ($[M+H]^+$, 1), 353 (100), 333 (75); FAB-HRMS calcd for $C_{24}H_{30}O_4NaSi$ $[M+Na]^+$, 433.1811; found 433.1848.

Ethyl (2*E*)(5*S*)-5-*tert*-Butyldiphenylsilyloxy-6-oxohept-2-enoate (12): A 1.4 M THF solution of MeMgBr (1.13 mL) was added to a stirred solution of **11** (476 mg, 1.16 mmol) in dry hexane (5 mL) and Et_2O (10 mL) at -78°C, and the reaction mixture was gradually warmed to rt during 12 h, the reaction was quenched with sat. aqueous NH_4Cl solution. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 5 /1) to afford alcohol (220 mg, 44%) as a colorless oil.

A solution of DMSO (146 μL, 2.60 mmol) in dry CH_2Cl_2 (10 mL) was added to a stirred solution of oxalyl chloride (90 μL, 1.30 mmol) at -78°C. After 15 min, a CH_2Cl_2 (3 mL) solution of the above alcohol (220 mg, 0.52 mmol) was added to the reaction mixture. Stirring was continued for 15 min at -78°C, and then Et_3N (431 μL, 3.9 mmol) was added. After 30 min at -78°C, the reaction mixture was quenched with sat. aqueous NH_4Cl solution. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 10 /1) to afford **12** (191 mg, 88%) as a colorless oil: Rf = 0.30 (hexane/EtOAc, 7/1); ^{1}H-NMR (100 MHz, $CDCl_3$) 7.64-7.59 (4H, m), 7.44-7.42 (2H, m), 7.40-7.36 (4H, m), 6.84 (1H, dt, *J* = 15.6, 7.6 Hz), 5.74 (1H, ddd, *J* = 1.2, 1.5, 15.6 Hz), 4.24 (1H, dd, *J* = 5.4, 6.1 Hz), 4.17 (2H, q, *J* = 7.0 Hz), 2.46 (1H, dddd, *J* = 1.2, 5.4, 7.6, 14.4 Hz), 2.37 (1H, dddd, *J* = 1.5, 6.1, 7.6, 14.4 Hz), 2.08 (3H, s), 1.27 (3H, t, *J* = 7.0 Hz), 1.12 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) 210, 165.8, 142.5, 135.79, 135.75, 132.9, 132.5, 130.12, 130.10, 1327.9, 127.8, 124.6, 78.0, 60.2, 37.3, 26.9, 26.1, 19.3, 14.2; IR (neat, cm^{-1}) 2934 (s), 2859 (s), 1723 (s), 1657 (m), 1590 (w), 1474 (m), 1428 (s), 1368 (m), 1267 (s), 1165 (s), 1113 (s), 1044 (m), 834 (m), 741 (m), 702 (s); FAB-MS (m/z) 449 (4), 448 (6), ($[M+Na]^+$, 18), 411 ($[M+H]^+$, 1), 367 (49), 347 (50), 254 (18), 235 (21), 135 (100); FAB-HRMS calcd for

$C_{25}H_{32}O_4NaSi$ $[M+Na]^+$, 447.1968; found 447.2004.

Ethyl (2*E*,6*E*)(5*S*)-5-*tert*-Butyldiphenylsilyloxy-6-methyl-7-{2-methyl-(1,3-thiazol-4-yl)}hepta-2,6-dienoate (14): A 1.54 M n-BuLi solution in hexane (0.34 mL, 0.52 mmol) was added to a stirred solution of **13** (158 mg, 0.63 mmol) in dry THF (2 mL) at -78°C. After 30 min, a solution of **12** (134 mg, 0.32 mmol) in dry THF (1 mL) was added dropwise, and the reaction mixture was gradually warmed to rt during 11 h. The reaction was quenched with sat. aqueous NH_4Cl solution (10 mL), and the mixture was extracted with EtOAc (25 mL x 3). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 6 /1) to afford **14** (46 mg, 28%) as a colorless oil: Rf = 0.29 (hexane/EtOAc, 7/1); $[\alpha]_D^{25}$ = -25.2° (*c* 1.6, $CHCl_3$); ^{1}H-NMR (100 MHz, $CDCl_3$) 7.68-7.60 (4H, m), 7.43-7.34 (4H, m), 7.32-7.28 (2H, m), 6.79 (1H, dt, 15.7, 7.5 Hz), 6.78 (1H, s), 6.28 (1H, s), 5.69 (1H, ddd, *J* = 15.5, 5.6 Hz), 5.42 (1H, dt, *J* =15.5, 6.6 Hz), 4.23 (1H, dd, *J* =5.3, 6.4 Hz), 3.92 (1H, d, *J* = 1.2, 1.6, 15.7 Hz), 4.28 (1H, t, *J* = 6.1 Hz), 4.12 (2H, q, *J* = 7.1 Hz), 2.69 (3H, s), 2.45 (1H, dddd, *J* = 1.6, 6.1, 7.5, 14.4 Hz), 2.39 (1H, dddd, *J* = 1.2, 6.1, 7.5, 14.4 Hz), 1.98 (3H, d, *J* = 1.0 Hz), 1.24 (3H, t, *J* = 7.1 Hz), 1.08 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) 166.2, 162.3, 152.8, 144.8, 140.0, 135.97, 135.92, 133.9, 133.5, 129.7, 129.6, 127.6, 127.5, 123.4, 120.0, 115.7, 78.0, 60.1, 39.4, 27.0, 19.4, 19.2, 14.2, 14.1; IR (neat, cm^{-1}) 2932 (m), 2859 (m), 1721 (s), 1655 (w), 1474 (m), 1427 (m), 1368 (m), 1314 (m), 1267 (m), 1181 (m), 1159 (m), 1111 (s), 1071 (s), 1046 (s), 822 (m), 741 (m), 702 (s); FAB-MS (m/z) 542 ($[M+Na]^+$, 9), 522 (11), 521 (26), 520 ($[M+H]^+$, 68), 406 (62), 197 (39), 135 (100); FAB-HRMS calcd for $C_{30}H_{38}NO_3SSi$ $[M+H]^+$, 520.2359; found 520.2342.

(2*E*,6*E*)(5*S*)-5-*tert*-Butyldiphenylsilyloxy-6-methyl-7-{2-methyl-(1,3-thiazol-4-yl)}hepta-2,6-dienal (15): To a solution of **14** (23.3 mg, 0.046 mmol) in CH_2Cl_2 (20 mL) was added 1M CH_2Cl_2 solution of DIBAL (0.15 mL, 0.15 mmol) at -78°C. After 30 min at -78°C, the reaction mixture was warmed to rt and then the reaction was quenched with sat. aqueous NH_4Cl solution. The reaction mixture was diluted with $CHCl_3$, and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated *in vacuo*. Purification of the residue was accomplished by silica gel preparative TLC (hexane/EtOAc, 2/1) to afford a 22 mg (98 %) of (2*E*,6*E*)(5*S*)-5-*tert*-butyldiphenylsilyloxy-6-methyl-7-{2-methyl-(1,3-thiazol-4-yl)}hepta-2,6-dien-1-ol as a colorless oil: Rf = 0.11 (hexane/EtOAc, 2/1); ^{1}H-NMR (100 MHz, $CDCl_3$) 7.71-7.69 (2H, m), 7.64-7.62 (2H, m), 7.45-7.36 (4H, m), 7.33-7.30 (2H, m), 6.79 (1H, s), 6.26 (1H, s), 5.50 (1H, dt, *J* = 15.5, 5.6 Hz), 5.42 (1H, dt, *J* = 15.5, 6.6 Hz), 4.23 (1H, dd, *J* = 5.3, 6.4 Hz), 3.92 (1H, d, *J* = 5.1 Hz), 2.69 (3H, s), 2.31-2.23 (2H, m), 1.94 (3H, s), 1.07 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) 164.5, 152.8, 140.9, 136.0, 135.9, 134.3, 133.8, 131.6, 129.6, 129.5, 128.9, 127.5, 127.4, 119.8, 115.1, 78.7, 63.7, 39.2, 27.0, 19.4, 19.1, 14.1; IR (neat, cm^{-1}) 3360 (m), 2960 (s), 2930 (s), 2857 (s), 1590 (w), 1507 (m), 1472 (m), 1428 (s), 1186 (m), 1111 (s), 1071 (s), 970 (s), 822 (s); FAB-MS (m/z) 480 (6), 479 (15), 478 ($[M+H]^+$, 38), 407 (42), 406 (100), 199 (55), 198 (58), 135 (99); FAB-HRMS calcd for $C_{28}H_{36}NO_2SSi$ $[M+H]^+$, 478.2236; found 478.2212.

Dess-Martin periodinane (39 mg, 0.092 mmol) was added to a stirred solution of the above alcohol (22

mg, 0.046 mmol) in CH_2Cl_2 (1 mL). After being stirred for 40 min, the reaction mixture was quenched by adding of sat. aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with EtOAc (10 mL x 3), and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (hexane/EtOAc, 3/1) to give **15** (21.0 mg, 96%) as a colorless oil: Rf = 0.46 (hexane/EtOAc, 3/1); ^{1}H-NMR (100 MHz, $CDCl_3$) 9.28 (1H, dd, *J* = 1.2, 7.8 Hz), 7.70-7.67 (2H, m), 7.92-7.60 (2H, m), 7.45-7.30 (6H, m), 6.85 (1H, s), 6.57 (1H, dt, *J* = 15.5, 7.3 Hz), 6.40 (1H, s), 5.95 (1H, ddd, *J* = 1.8, 7.8, 15.5 Hz), 4.36 (1H, t, *J* = 6.0 Hz), 2.71 (3H, s), 2.60-2.46 (2H, m), 2.03 (3H, s), 1.09 (9H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) 193.8, 164.9, 154.1, 152.3, 140.6, 134.8, 119.7, 116.2, 76.1, 38.3, 19.2, 14.3 ; IR (neat, cm^{-1}) 2932 (s), 2857 (s), 1692 (s), 1587 (w), 1472 (m), 1428 (s), 1184 (m), 1111 (s), 1073 (s), 976 (m), 822 (m), 741 (m), 702 (s) ; FAB-MS (m/z) 498 ($[M+Na]^+$, 21), 478 (6), 477 (14), 476 ($[M+H]^+$, 36), 406 (91), 197 (39), 176 (34), 154 (67), 135 (100); FAB-HRMS calcd for $C_{28}H_{34}NO_2SSi$ $[M+H]^+$, 476.2080; found 476.2069.

(2*E*,6*E*)(5*S*)-5-Hydroxy-6-methyl-7-{2-methyl-(1,3-thiazol-4-yl)}hepta-2,6-dienal (3): A stirred solution of **15** (19.0 mg, 0.04 mmol) and AcOH (14 μL, 0.25 mmol) in THF (1 mL) was added 1M THF solution of tetrabutyl ammonium fluoride (TBAF) (200 mL, 0.2 mmol) at rt. After stirring at rt for 15 h, the mixture was diluted with ether (10 mL). The mixture was washed with brine and sat. aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 1/1 to 1/2) to afford **3** (5.7 mg, 60 %) as a colorless oil: Rf = 0.11 (hexane/EtOAc, 1/1); ^{1}H-NMR (100 MHz, $CDCl_3$) 9.51 (1H, d, *J* = 7.8 Hz), 6.97 (1H, s), 6.90 (1H, dt, *J* =15.5, 7.1 Hz), 6.59 (1H, s), 6.21 (1H, ddt, *J* = 7.8, 15.4, 1.4 Hz), 4.37 (1H, t, *J* = 6.4 Hz), 2.75 (3H, s), 2.68 (1H, ddd, *J* = 1.5, 6.4, 7.8 Hz), 2.07 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) 193.9, 164.9, 154.1, 152.3, 140.0, 134.8, 119.7, 116.2, 76.1, 38.3, 19.2, 14.3; IR (neat, cm^{-1}) 3360 (m), 2926 (s), 2855 (m), 1686 (s), 1509 (m), 1184 (m), 1130 (m), 974 (m); FAB-MS (m/z) 240 (9), 239 (19), 220 ($[M+H]^+$, 72), 220 (26), 186 (51), 168 (100), 149 (82), 135 (75); FAB-HRMS calcd for $C_{12}H_{15}NO_2S$ $[M+H]^+$, 238.0902; found 238.0895.

4-Formyl-1(*R*)-{1-methyl-2-[2-methyl(1,3-thiazol-4-yl)]-1(*E*)-ethenyl}-3(*E*)-butenyl (3*R*,4*S*,5*S*,6*R*,8*R*)-10-Dimethoxyphosphono-6-{2-(*tert*-butyldiphenylsilyloxy)ethyl}-3,5-isopropylidenedioxy-3,8-dimethyl-9-oxodecanoate (16): A solution of **7** (60 mg, 0.91 mmol), 2-methyl-2-butene (48 μL, 0.45 mmol), NaH_2PO_4 (44 mg, 0.36 mmol) and $NaClO_2$ (33 mg, 0.36 mmol) in *t*-BuOH (3 mL) and H_2O (1 mL) were stirred at rt for 10 min, the reaction mixture was extracted with CH_2Cl_2 (20 mL x 3). The combined organic layers were washed with sat. aqueous 1M HCl solution and brine, dried (Na_2SO_4), then filtered. Concentration of the filtrate *in vacuo* afforded (3*R*,4*S*,5*S*,6*R*,8*R*)-10-dimethoxyphosphono-6-{2-(*tert*-butyldiphenylsilyloxy)ethyl}-3,5-isopropylidenedioxy-3,8-dimethyl-9-oxodecanoic acid (**2**, 62.0 mg, 100%) as a colorless oil which was used in the next reaction without further purification.

A stirred solution of **2** (62.0 mg, 0.092 mmol) and Et_3N (38 mL, 0.14 mmol) in THF (2 mL) was added 2,4,6-trichlorobenzoyl chloride (22 mL, 0.14 mmol) under nitrogen atmosphere at rt. After stirring at rt for

60 min, the precipitated inorganic salt was filtered off and the filtrate was evaporated *in vacuo* to leave an oil, which was dissolved in toluene (1 mL). To this stirred solution, a solution mixture of **3** (21.0 mg, 0.089 mmol) and DMAP (13.2 mg, 0.092 mmol) in toluene (1.0 mL) was added. The reaction mixture was stirred for 23 h at rt and the mixture was diluted with ether (10 mL). The mixture was washed with brine and sat. aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 1/2) to afford **16** (60.3 mg, 76%) as a colorless oil: Rf = 0.08 (hexane/EtOAc, 1/2); ^{1}H-NMR (400 MHz, $CDCl_3$) 9.49 (1H, d, *J* = 7.8 Hz), 7.65-7.63 (4H, m), 7.42-7.35 (6H, m), 7.13 (1H, s), 6.75 (1H, dt, *J* = 15.6, 6.7 Hz), 6.54 (1H, s), 6.17 (1H, dd, *J* = 7.8, 15.6 Hz), 5.46 (1H, t, *J* = 6.6 Hz), 4.32-4.26 (1H, m), 3.75 (6H, d, *J* = 11.2 Hz), 3.76-3.59 (3H, m), 3.09 (1H, d, *J* = 22.2 Hz), 2.90-2.82 (1H, m), 2.80 (1H, t, *J* = 6.7 Hz), 2.76 (1H, t, *J* = 6.7 Hz), 2.69 (3H, s), 2.57 (1H, dd, *J* = 9.0, 15.4 Hz), 2.30 (1H, dd, *J* = 3.9, 15.4 Hz), 2.09 (3H, s), 1.73-1.65 (2H, m), 1.60-1.51 (1H, m), 1.50-1.45 (1H, m), 1.36 (3H, s), 1.73-1.65 (2H, m), 1.60-1.51 (1H, m), 1.50-1.45 (1H, m), 1.36 (3H, s), 1.35-1.30 (1H, m), 1.34 (3H, s), 1.15-1.05 (1H, m), 1.03 (9H, s), 1.00 (3H, d, *J* = 6.8 Hz), 0.82 (3H, d, *J* = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 205.8, 193.4, 170.4, 152.1, 152.0, 135.7, 135.5, 138.1, 138.5, 129.7, 127.7, 121.3, 116.8, 99.0, 77.8, 76.9, 70.1, 60.7, 52.9 (x2), 46.9, 38.9 (d, *J* = 132.1 Hz),), 38.7, 36.3, 34.6, 33.7, 32.8, 32.2, 29.7, 26.8, 19.4, 19.2, 19.0, 15.7, 14.6, 5.0; IR (neat, cm^{-1}) 2960 (m), 2930 (m), 2857 (m), 1738 (s), 1735 (s), 1715 (s), 1694 (s), 1591 (w), 1462 (m), 1429 (m), 1380 (m), 1263 (m), 1181 (s), 1111 (s), 1034 (s), 1015 (s), 823 (m), 737 (s), 704 (s); FAB-MS (m/z) 919 (17), 918 ($[M+Na]^+$, 29), 897 (4), 896 ($[M+H]^+$, 7), 838 (10), 220 (85), 151 (100); FAB-HRMS calcd for $C_{47}H_{67}NO_{10}PSSi$ $[M+H]^+$, 896.3993; found 896.4026.

(4*R*,5*S*,6*S*,7*R*,9*R*,16*S*)-7-{2-(*tert*-Butyldiphenylsilyloxy)ethyl}-4,6-isopropylidenedioxy-5,9-dimethyl-{1-methyl-2-{2-methyl-(1,3-thiazol-4-yl)}-1(*E*)-ethenyl}-11(*E*),13(*E*)-diene-2,10-dione (17): A mixture of **16** (31.5 mg, 0.035 mmol), K_2CO_3 (29.0 mg, 0.21 mmol) and 18-crown-6 (111.5 mg, 0.42 mmol, 12 equiv.) in toluene (35 mL, 1 mM solution) was stirred at rt for 22.5 h. After the reaction mixture was cooled to rt, sat. aqueous NH_4Cl solution (30 mL) was added to the mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with sat. aqueous KCl (60 mL x 2), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 9/1) to afford 16-membered ring lactone (17) (12.5 mg, 46 %) as a colorless oil from the first fraction and conjugate aldehyde (**18**) (1.2 mg, 16 %) as a colorless oil from the second fraction: Data for **17**; $[\alpha]_D^{24}$ = -49° (*c* 0.6, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$) 7.68-7.65 (4H, m), 7.44-7.37 (6H, m), 7.08 (1H, dd, *J* = 10.5, 15.4 Hz), 6.96 (1H, s), 6.55 (1H, s), 6.39 (1H, d, *J* = 15.4 Hz), 6.25 (1H, dd, *J* = 10.5, 15.1 Hz), 6.04 (1H, ddd, *J* = 4.8, 10.0, 15.1 Hz), 5.42 (1H, dd, *J* = 2.0, 11.0 Hz), 4.01 (1H, dt, *J* = 1.0, 6.1 Hz), 3.76 (1H, d, *J* = 2.9 Hz), 3.65 (1H, dt, *J* = 6.6, 10.0 Hz), 3.58 (1H, dt, *J* = 6.6, 10.0 Hz), 2.70 (3H, s), 2.63-2.57 (2H, m), 2.51 (1H, dd, *J* = 11.0, 14.2 Hz), 2.39 (2H, d, *J* = 6.1 Hz), 2.11 (3H, s), 1.94-1.86 (1H, m), 1.75 (1H, ddd, *J* = 6.5, 10.2, 14.8 Hz), 1.65-1.55 (1H, m), 1.41 (1H, dt, *J* = 5.2, 14.8 Hz), 1.36-1.23 (2H, m), 1.34 (3H, s), 1.26 (3H, s), 1.14 (3H, d, *J* = 6.8 Hz), 1.05 (9H, s), 0.93 (3H, d, *J* = 6.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 204.7, 170.9, 164.9, 152.3, 140.8, 138.8, 137.1, 135.6, 133.9, 132.2, 129.6, 127.6, 126.4, 120.3, 116.6, 99.9, 77.2, 77.0, 73.1,

62.8, 46.4, 39.2, 38.6, 38.4, 34.8, 34.6, 33.7, 29.6, 26.9, 19.8, 19.2, 19.2, 17.1, 15.1, 7.0; IR (neat, cm^{-1}) 2990 (m), 2960 (s), 2930, 2869, 1735 (s), 1684 (s), 1636 (w), 1593 (s), 1458 (m), 1429 (s), 1379 (s), 1264 (s), 1198 (s), 1159 (s), 1111 (s), 1085 (s), 1010 (s), 1000 (s), 824 (m), 756 (s), 740 (s), 704 (s); FAB-MS (m/z) 772 (3), 771 (7), 770 ($[M+H]^+$, 12), 712 (100); FAB-HRMS calcd for $C_{45}H_{60}NO_6SSi$ $[M+H]^+$, 770.3911; found 770.3936.

(4*R*,5*S*,6*S*,7*R*,9*R*,16*S*)-7-(2-Hydroxyethyl)-4,6-isopropylidenedioxy-5,9-dimethyl-{1-methyl-2-{2-methyl-(1,3-thiazol-4-yl)}-1(*E*)-ethenyl}-11(*E*),13(*E*)-diene-2,10-dione (19): To a stirred solution of **18** (11.5 mg, 0.015 mmol) and AcOH (8.4 mL, 0.15 mmol) in THF (1 mL) was added 1M THF solution of TBAF (90 mL, 0.09 mmol) at rt. After stirring at rt for 48 h, the mixture was diluted with ether (10 mL). The mixture was washed with brine and sat. aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 1/1 to 1/2) to afford **19** (6.8 mg, 86 %) as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) 7.08 (1H, dd, *J* = 10.7, 15.2 Hz), 6.98 (1H, s), 6.55 (1H, s), 6.42 (1H, d, *J* = 15.2 Hz), 6.26 (1H, dd, *J* = 10.7, 15.2 Hz), 6.06 (1H, ddd, *J* = 4.8, 10.0, 15.2 Hz), 5.45 (1H, dd, *J* = 2.5, 10.7 Hz), 4.09 (1H, dt, *J* = 2.0, 6.3 Hz), 3.83 (1H, dd, *J* = 1.5, 3.6Hz), 3.67-3.54 (2H, m), 2.71 (3H, s), 2.67-2.59 (2H, m), 2.53 (1H, dt, *J* = 13.9, 10.5 Hz), 2.44 (1H, dd, *J* = 6.3, 14.5 Hz), 2.40 (1H, dd, *J* = 6.6, 14.5 Hz), 2.11 (3H, s), 1.89 (1H, dq, *J* = 14.2, 6.1 Hz), 1.84 (1H, ddd, *J* = 5.9, 10.3, 15.4 Hz), 1.62-1.54 (1H, m), 1.45 (1H, dt, *J* = 14.2, 6.1 Hz), 1.40 (3H, s), 1.40-1.35 (1H, m), 1.38 (3H, s), 1.31 (1H, tq, *J* = 2.0, 6.8 Hz), 1.20 (3H, d, *J* = 6.7 Hz), 0.99 (3H, d, *J* = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 205.0, 170.7, 164.9, 152.2, 141.3, 139.2, 137.0, 132.0, 126.2, 120.4, 116.7, 100.3, 77.1, 74.4, 73.1, 61.1, 46.5, 38.9, 38.8, 38.3, 35.2, 34.8, 34.2, 29.5, 19.7, 19.2, 17.0, 15.1, 7.1; FAB-MS (m/z) 534 (6), 533 (17), 532 ($[M+H]^+$, 44), 474 (24), 413 (50), 391 (64), 149 (10ß0); FAB-HRMS calcd for $C_{29}H_{42}NO_6S$ $[M+H]^+$, 532.2733; found 532.2695.

(4*R*,5*S*,6*S*,7*R*,9*R*,16*S*)-7-Formylmethyl-4,6-isopropylidenedioxy-5,9-dimethyl-{1-methyl-2-{2-methyl-(1,3-thiazol-4-yl)}-1(*E*)-ethenyl}-11(*E*),13(*E*)-diene-2,10-dione (20): Dess-Martin periodinane (20.0 mg, 0.045 mmol) was added to a stirred solution of **19** (6.0 mg, 0.011 mmol) in CH_2Cl_2 (1 mL). After being stirred for 1 h, the reaction mixture was quenched by adding of sat. aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with EtOAc (10 mL x 3), and combined organic layers were washed with brine, dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (hexane/EtOAc, 2/1) to give **20** (3.8 mg, 63%) as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) 9.67 (1H, t, *J* = 1.6 Hz), 7.16 (1H, dd, *J* = 10.5, 15.3 Hz), 6.98 (1H, s), 6.57 (1H, s), 6.37 (1H, d, *J* = 15.3 Hz), 6.26 (1H, dd, *J* = 10.5, 14.9 Hz), 6.09 (1H, ddd, *J* = 4.9, 10.0, 14.9 Hz), 5.46 (1H, dd, *J* = 1.9, 11.0 Hz), 4.03 (1H, dt, *J* = 1.5, 5.6 Hz), 3.87 (1H, dd, *J* = 1.0, 4.4 Hz), 2.80 (1H, ddd, *J* = 1.7, 4.9, 16.4 Hz), 2.72 (3H, s), 2.64 (1H, ddd, *J* = 1.9, 4.9, 13.7 Hz), 2.52 (1H, ddd, *J* = 10.0, 11.0, 13.7 Hz), 2.41 (1H, dd, *J* = 5.6, 14.0 Hz), 2.38 (1H, dd, *J* = 5.6, 14.0 Hz), 2.30-2.25 (1H, m), 2.19 (1H, ddd, *J* = 2.0, 8.0, 16.3 Hz), 2.11 (3H, s), 1.78 (1H, ddd, *J* = 8.1, 9.0, 14.6 Hz), 1.40-1.32 (2H, m), 1.37 (3H, s), 1.36 (3H, s), 1.20 (3H, d, *J* = 6.8 Hz), 0.93 (3H, d, *J* = 6.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 203.9, 201.8, 171.7, 165.1, 152.2, 141.4, 139.3, 137.3, 132.0, 125.7, 120.1, 116.6, 100.2, 76.8, 72.8, 72.6,

46.9, 16.1, 39.2, 38.4, 36.1, 34.5 (x2), 29.4, 19.7, 19.1, 16.7, 15.2, 7.2; IR (neat, cm^{-1}) 2990 (m), 2928 (m), 2857 (m), 2726 (w), 1738 (s), 1730 (s), 1682 (s), 1634 (m), 1592 (s), 1507 (w) 1456 (m), 1381 (s), 1350 (m), 1264 (s), 1200 (s), 1160 (s), 1053 (m), 1009 (s), 982 (s), 737 (s); FAB-MS (m/z) 532 (14), 531 (37), 530 ($[M+H]^+$, 100), 472 (35); FAB-HRMS calcd for $C_{29}H_{40}NO_6S$ $[M+H]^+$, 530.2576; found 530.2545.

Hybrid macrolide hemiacetal (1): A solution of **20** (2.0 mg, 3.8 mmol) in 1N HCl (0.25 mL) and THF (0.75 mL) was stirred at 50°C for 5 h. The reaction mixture was neutralized with solid $NaHCO_3$, and then evaporated to dryness. The residue was partitioned between CH_2Cl_2 (10 mL) and water (5 mL). The separated aqueous layer was further extracted with CH_2Cl_2 (10 mL x 2). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc, 1/1) to afford **1** (1.2 mg, 65%) as a solid: ^{1}H-NMR (400 MHz, $CDCl_3$) 7.21 (1H, dd, *J* = 10.3, 15.1 Hz), 7.00 (1H, s), 6.61 (1H, s), 6.43 (0.25H, d, *J* = 15.4 Hz), 6.39 (0.75H, d, *J* = 15.1 Hz), 6.20 (0.25H, dd, *J* = 10.0, 15.0 Hz), 6.19 (0.75H, *J* = 10.0, 15.0 Hz), 5.59 (1H, dd, *J* = 1.6, 11.1 Hz), 5.51 (1H, t, *J* = 3.8 Hz), 4.12 (1H, dd, *J* = 3.6, 6.3 Hz), 3.83 (0.25 H, s, OH), 3.80 (0.75H, s, OH), 3.65 (1H, d, *J* = 11.2 Hz), 2.74 (3H, s), 2.67 (1H, ddd, *J* = 1.6, 4.2, 13.2 Hz), 2.62 (1H, dd, *J* = 11.5, 16.6 Hz), 2.53-2.45 (1H, m), 2.42 (1H, ddd, *J* = 10.0, 11.0, 13.2 Hz), 2.19-2.10 (1H, m), 2.15 (1H, d, *J* = 16.6 Hz), 2.11 (3H, s), 1.97-1.84 (2H, m), 1.70-1.63 (1H, m), 1.60-1.40 (1H, m), 1.22 (3H, d, *J* = 7.0 Hz), 1.03 (3H, d, *J* = 6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) 203.4, 173.8, 162.9, 158.0, 141.6, 139.2, 135.6, 132.8, 124.0, 120.2, 116.6, 97.1, 81.4, 76.1, 66.7, 45.8, 40.4, 38.8, 38.6, 37.8, 37.0, 33.0, 19.0, 17.6, 15.3, 9.6; IR (neat, cm^{-1}) 3507 (m), 2926 (m), 2857 (m), 1746 (s), 1737 (s), 1681(s), 1634 (m), 1595 (s), 1507 (m), 1456 (m), 1352 (m), 1269 (s), 1182 (s), 1005 (s), 884 (m), 787 (s); FAB-MS (m/z) 512 ($[M+Na]^+$, 25), 491 (24), 490 ($[M+H]^+$, 72), 472 (100); FAB-HRMS calcd for $C_{26}H_{36}NO_6S$ $[M+H]^+$, 490.2263; found 490.2271.

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8. In order to form macrorings efficiently, macrolactonization is the most popular method, but the Horner-Emmons cyclization[11] gave much better results for the synthesis of enone and dienone-type macrolides, and this methodology is now established.
9. Unless otherwise noted, the numberings are based on carbonolide.
10. Another C11-C21 fragment having a DMPM group at the C15 hydroxy group instead of TBDPS was similarly synthesized from **8**. However, deprotection of the DMPM group in the presence of thiazole functionality obtained poor results to afford **3** only in 11 %.
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