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Studies on the synthesis of DNA-damaging part of leinamycin: regioselectivity in Ti(O*i*Pr)$_4$ mediated opening of hydroxy epoxides with carboxylic acids

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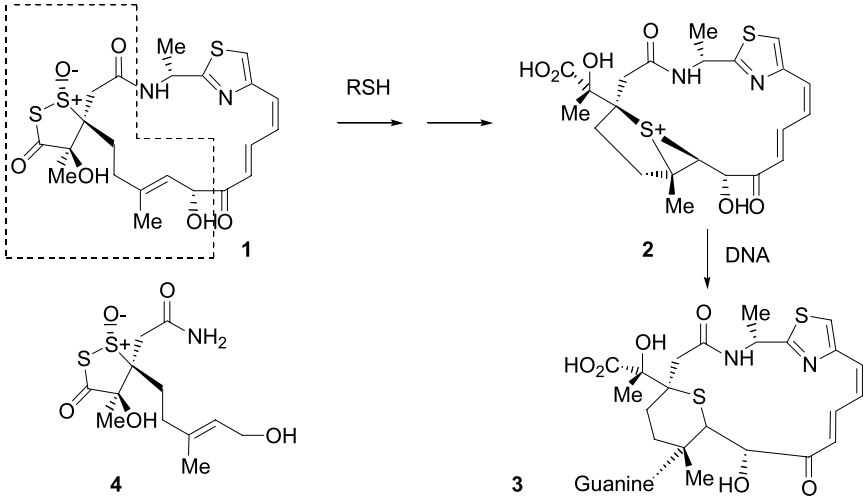
Abstract—The preparation of the key intermediate in the synthesis of the DNA damaging fragment of the anticancer antibiotic leinamycin starting from geraniol is described. The synthetic sequence involves the building of a quaternary asymmetric center through kinetic resolution through Sharpless epoxidation followed by the regioselective opening of the resultant enantiomerically pure hydroxyepoxide and intramolecular Wittig–Horner olefination.

1. Introduction

Leinamycin **1** is a highly potent macrocyclic anticancer antibiotic possessing a spiro-1, 3-dioxo-1, 2-dithiolane functionality (Scheme 1).[1] Leinamycin shows a high antiproliferative activity against a number of models such as human uterine carcinoma and murine leukemia.[2] It is unique among other DNA damaging compounds by having a dual mechanism of action working as a DNA alkylating agent[3] and also as a source of free radicals.

Reaction of intracellular thiols such as glutathione with leinamycin triggers a sequence of transformations resulting in the production of episulfonium cation of type **2** (Scheme 1). Cation **2** is capable of subsequent alkylation of guanine units of DNA resulting in a fast DNA strand



Scheme 1.

Keywords: Leinamycin; Sharpless epoxidation; Epoxide opening; Wittig–Horner olefination.
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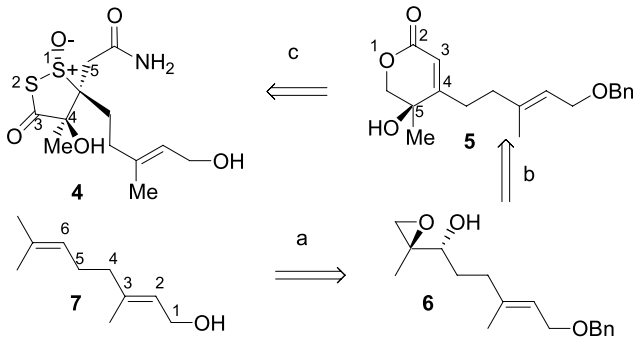


Scheme 2.

scission.[3] Formation of episulfonium cation **2** is accompanied by the formation of hydroxydisulfides that according to Gates[4] produce hydroxy radicals in the subsequent reaction with molecular oxygen hydroxy radicals that are capable of augmenting DNA damage from the above mentioned alkylation reaction.

From the chemical point of view it can be assumed that the DNA damaging activity of leinamycin is concentrated in the fragment of type **4**. The rest of the leinamycin molecule including the conjugated polyalkylidene chain and the thiazole cycle are most probably responsible for the binding with DNA.[5] This assumption may have a substantial importance for the design of new analogs of leinamycin possessing antineoplastic activity. These compounds will be of substantial practical interest since the use of leinamycin itself as an anticancer drug is seriously complicated by its low availability and stability in water solutions.[6] A number of semisynthetic leinamycin derivatives have been prepared in order to enhance its stability.[6] The radical solution, however, could involve the production of completely new leinamycin derivatives by the attachment of the DNA damaging fragment of type **4** to known DNA binding intercalators such as polycyclic heteroaromatic compounds.[7]

The synthesis of the DNA damaging part of leinamycin therefore constitutes a substantial interest. The only known synthesis of leinamycin[8] does not give a possibility for a separate synthesis of fragments of type **4**. A number of simple leinamycin mimetics have been synthesized.[9] However, these compounds contain only part of the necessary functions of the DNA damaging fragment **4** and therefore do not possess substantial DNA alkylating activity.

2. Results and discussion

Our approach toward the DNA damaging part of leinamycin **4** (Scheme 2) was based on commercially available geraniol **7** possesses all except two carbon atoms of fragment **4**. The synthetic plan for the preparation of **4** involved three main stages: (a) stereocontrolled formation of hydroxyepoxide **6**; (b) the attachment of two carbon units to the carbon skeleton of geraniol; (c) stereocontrolled introduction of sulfur atoms to C-4 of the key unsaturated lactone **5** followed by the formation of 1,3-dioxo-1,2-dithiolane cycle.

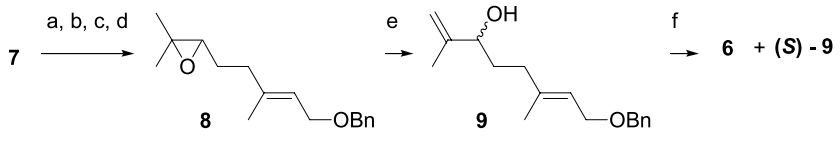
Two possible approaches towards the asymmetric functionalization of geraniol **7** at position 6 had been reported, both starting from the conversion of geraniol into monoepoxide of type **8** (Scheme 3). The first approach involved the hydrolysis of epoxide **8** to give the corresponding racemic diol which had been deracemized through the oxidation of the secondary hydroxy group followed by the baker yeast reduction.[10,11] The alternative approach[12] involved the isomerization of epoxides of type **8** into racemic allyl alcohols of type **9** followed by Sharpless epoxidation under kinetic resolution conditions.[13]

While the second approach is based on kinetic resolution and therefore should provide a lower theoretical yield, it is substantially more convenient than the microbiogical process. In line with this approach we converted geraniol **7** into racemic allyl alcohol **9** through sequential acetylation, hydroxy-bromination, epoxide ring closure, benzyl protection, and acid catalyzed rearrangement of the resultant epoxide **8** into racemic alcohol **9** (Scheme 3). While a number of protic and Lewis acids were found to catalyze the rearrangement of epoxide **8** (stage (e), Scheme 3), we found that the catalysis with aluminium isopropoxide[14] provided a much better yield than protic acids. Catalysis by titanium isopropoxide provided similarly high chemoselectivity but substantially lower reaction rates.

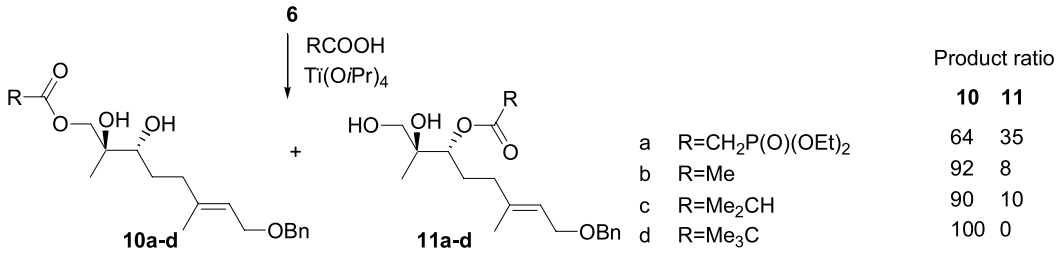
Sharpless epoxidation of racemic allyl alcohol **9** using (−)-DIPT and 0.45 equiv of *t*-BuOOH proceeded with a high enantio- (98%) and diastereoselectivity (>98%) thus providing hydroxyepoxide **6** with 45% yield and recovered predominantly (*S*)-allyl alcohol **9**.[15]

The conversion of hydroxyepoxide **6** into unsaturated lactone **5** was planned to involve a regioselective opening of the epoxide ring, oxidation of the resultant hydroxyepoxide function, and intramolecular Witting–Horner olefination.

The Ti(O*i*Pr)$_4$ mediated opening of hydroxyepoxides has been first reported by Sharpless.[16] Among other nucleophiles, carboxylic acids have been found to open hydroxyepoxides with a high regioselectivity. A number of preparative applications of this reaction are known, all proceeding with high regioselectivity.[17] We planned to use this reaction for regioselective opening of the epoxide ring with simultaneous introduction of diethylphosphonoacetate



Scheme 3. Reagents and conditions: (a) Ac_2O, DMAP, 99%; (b) NBS, dioxane–water, 98%; (c) NaOH, MeOH, 97%; (d) NaH, BnBr, 98%; (e) Al(O*i*Pr)$_3$, toluene, 110 °C, 95%; (f) (−)-DIPT (0.1 equiv), *t*-BuOOH (0.45 equiv) Ti(O*i*Pr)$_4$, molecular sieves, −20 °C, 45%.



Scheme 4.

residue. However, all our attempts to open the epoxide cycle using Ti(O*i*Pr)$_4$ resulted in the production of 64:35 mixture of isomers **10a** and **11a** (Scheme 4).

The formation of isomer **11a** can be attributed to the transesterification of the initially formed diol **10a** thus providing a thermodynamic mixture of isomers. The transesterification of diols of type **10** in neutral reaction conditions has not been reported previously. However, since titanium alkoxides catalyzed transesterifications are well documented,[18] it is reasonable to suggest that Ti(O*i*Pr)$_4$ indeed participate in the process. In order to verify this, pure isomer **10a** was treated with equimolar amounts of Ti(O*i*Pr)$_4$ in dichloromethane. Indeed this reaction provided a mixture of isomers **10a** and **11a** with the same ca. 2:1 composition.

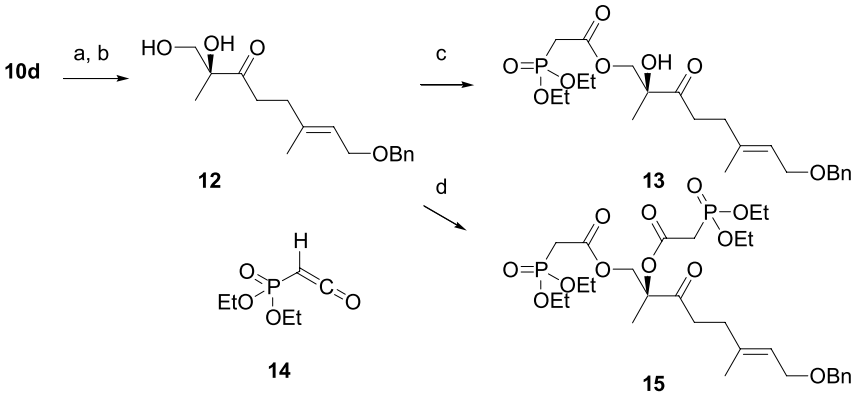
Our attempts to optimize the yield of diol **10a** using low temperatures and different reaction solvents were not successful as the equilibration between isomers **10a** and **11a** was found to proceed faster than the ring opening. Other methods of ring opening in hydroxyepoxide **6** in the absence of Ti(O*i*Pr)$_4$ such as reactions with cesium and potassium diethylphosphonoacetates[19] were also unsuccessful. Oxidation of hydroxyepoxide **6** into corresponding ketoepoxide followed by the treatment of cesium diethylphosphonoacetate up to 140 °C also did not provide desired products of epoxide ring opening.

It may be assumed that the observed transesterification is facilitated by the presence of the adjacent quaternary carbon atom. Such an arrangement should decrease the rate of nucleophilic attack on the epoxide ring due to steric effects, and in the same time increase the rate of transesterification due to Thorpe–Ingold-effect.

We have found, however, that the regioselectivity of Ti(O*i*Pr)$_4$ catalyzed ring opening in hydroxyepoxide **6** with different carboxylic acids is highly dependent on the structure of the carboxylic acids. Opening of hydroxyepoxide **6** with isobutyric and acetic acids proceeded with a substantial selectivity in favor of primary esters **10b**,**c**. The opening of hydroxyepoxide **6** with pivalic acid proceeded without any transesterification thus giving only desired ester **10d**.

Subsequent Swern oxidation of diol **10d** followed by the hydrolysis of pivaloyl group provided dihydroxy ketone **12** (Scheme 5). Initial attempts for acylating the primary hydroxy group of dihydroxy ketone **12** with diethylphosphonoacetyl chloride prepared from diethylphosphonoacetic acid (DEPA) by the treatment with triphosgene/collidine[20] failed, most probably due to the instability of diethylphosphonoacetyl chloride. Instead, the coupling was achieved by the treatment of a 1:1 mixture of DEPA and dihydroxy ketone **12** with 1 equiv of DCC without any acylation catalysts thus producing diethylphosphonoacetate ester **13**. These unusually mild reaction conditions that are usually not possible for conventional carbodiimide mediated esterifications went on in a high yield with DEPA since the acylation proceeded through the intermediacy of corresponding diethoxyphosphoryl ketene of type **14** (Scheme 5).[21] Ketenes with electron withdrawing substituents such as **14** possess a high reactivity and low sensitivity toward steric hindrance so that even the corresponding diacylation product (**15**) can be obtained if an excess of DEPA/DCC is used.

Our synthetic plan involved the cyclization of diethylphosphonoacetate ester **13** into the key unsaturated lactone of type **5** through intramolecular Wittig–Horner olefination.



Scheme 5. Reagents and conditions: (a) Oxalyl chloride, DMSO, Et$_3$N, 93%; (b) NaOH/MeOH, 97%; (c) DEPA (1 equiv), DCC (1 equiv), 93%; (d) DEPA (4 equiv), DCC (4 equiv), 95%.

Several examples of intramolecular Wittig–Horner olefination have been reported. Five- and six-membered unsaturated lactones have been prepared using NaH,[22] K_2CO_3,[23] and $LiClO_4$/DBU as a base.[24] The mildest reaction conditions involved the use of $LiClO_4$/iPr$_2$NEt.[25] In our attempts to obtain the intramolecular Wittig–Horner olefination products (Scheme 6), we tried the above mentioned reagents as well as potassium *tert*-butoxide and butyllithium. However, no traces of cyclization product were observed in all these reactions.

The total absence of cyclization products in these cases can be attributed to the presence of a hydroxy group in the α-position to the carbonyl group. Since pK_a of hydroxy groups in acyloins is about 14, the deprotonation of the tertiary hydroxy group in diethylphosphonoacetate ester **13** should proceed before the deprotonation of methylene group of the diethylphosphonoacetic moiety thus efficiently preventing the subsequent cyclization even if the deprotonation of the methylene group takes place.

To remove this obstacle the tertiary hydroxy group in diethylphosphonoacetate ester **13** was protected by silylation with an excess of chlorotrimethylsilane and hexamethyldisilazane. The subsequent treatment of *O*-silylated diethyl phosphonoacetate **16** with $LiClO_4$/DBU produced the desired lactone **17** although in a relatively low yield (up to 40%). Our attempts to optimize the reaction conditions as well as the use of other reagents mentioned above did not improve yields due to the formation of a number of byproducts. However, we were pleased to discover that a much higher yield (90%) of the intramolecular olefination can be achieved if *t*-BuOLi is used as a base for the reaction. The importance of lithium cation for the smooth deprotonation of phosphonoacetates is well documented[25] but to the best of our knowledge this is the first example of the use of *t*-BuOLi for Wittig–Horner olefination.

3. Conclusion

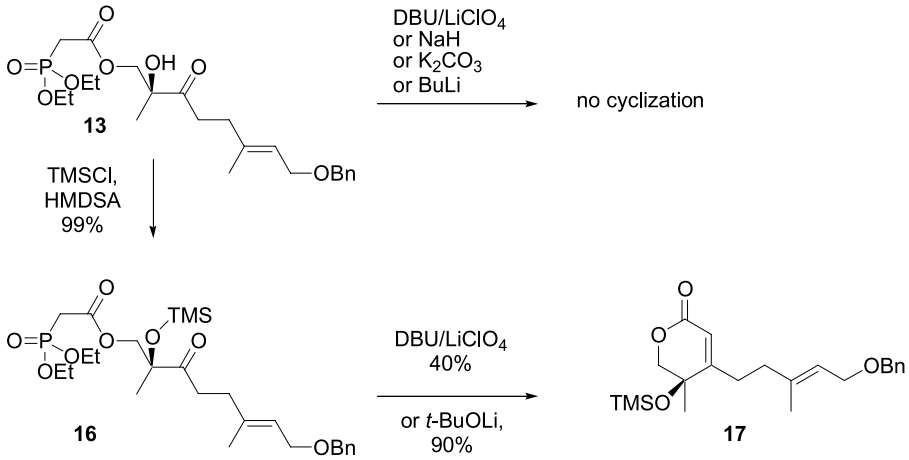
In conclusion, the key intermediate in the synthesis of DNA damaging fragment of leinamycin was synthesized from geraniol in 11 steps thus paving the road for a total synthesis of this fragment. The transesterification during titanium isopropoxide mediated epoxide ring opening with carboxylic acids was investigated and reaction conditions for achieving high regioselectivity were found. Intramolecular Wittig–Horner olefination was investigated and a new, more efficient reagent for the reaction was suggested.

4. Experimental

4.1. General information

Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254), flash chromatographic separations were performed on silica gel (Merck, Kieselgel 60, 230–400 Mesh ASTM). Medium pressure liquid chromatography (MPLC) was performed on glass columns (Buchi, B-685, $d=26$ mm, $l=460$ mm) with LiChroprep™ 60 (particle size 15–25 μm). Flash chromatography and MPLC were performed using only ethyl acetate–40–60 petroleum ether mixtures as the eluent. IR spectra were obtained with a Bruker Tensor 27 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX-300 spectrometer in $CDCl_3$ using the residual solvent peaks for calibration at rt. Optical rotation was measured by Jasco P-1010 polarimeter. Elementary analyses were performed by the microanalytical laboratory of the Hebrew University of Jerusalem, Jerusalem. High resolution mass-spectra were performed at the Technion on Bruker Daltonics APEX 3 instrument (CI). Unless otherwise stated, all reagents used are commercially available. Glassware was oven-dried before use and solvents were purified by conventional methods.

4.1.1. (3′*E*)-3-(5′-Benzyloxy-3′-methyl-pent-3′-enyl)-2,2-dimethyl-oxirane (8). To a solution of geraniol **7** (15.43 g, 100 mmol) in dichloromethane (50 mL) were added acetic anhydride (20 mL, 200 mmol) and DMAP (0.6 g, 5.0 mmol) at rt. The reaction mixture was stirred for 1 h, methanol (30 mL) was added, and additional 1 h stirring was carried out. The reaction mixture was dissolved in petrol ether, washed with water (2×30 mL) and saturated $NaHCO_3$ (2×30 mL), dried (Na_2SO_4) and evaporated to give the (2*E*)-Acetic acid 3,7-dimethyl-octa-2,6-dienyl ester as colorless oil (19.47 g, 99 mmol, 99%). ^{1}H NMR (300 MHz): 1.60 (s, 3H); 1.68 (s, 3H); 1.70 (s, 3H); 2.05 (s, 3H); 2.00–2.10 (m,



Scheme 6.

2H+2H); 4.59 (d, J=7 Hz, 2H); 5.08 (t, J=5 Hz, 1H); 5.42 (t, J=7 Hz, 1H). To a solution of the resultant (2*E*)-Acetic acid 3,7-dimethyl-octa-2,6-dienyl ester (36.31 g, 0.185 mol) in a mixture of dioxane (180 mL) and water (80 mL) was added dropwise a solution of *N*-bromosuccinimide (33.00 g, 0.185 mol) in dioxane (500 mL) at 0 °C for 2 h. The reaction mixture was stirred for additional 2 h at 0 °C, and 1 h at rt. The reaction mixture was concentrated to ca. 100 mL, dissolved in petroleum ether (100 mL), washed with brine (2×50 mL), dried (Na_2SO_4) and evaporated to give (2*E*)-Acetic acid 6-bromo-7-hydroxy-3,7-dimethyl-oct-2-enyl ester as pale yellow oil (53.09 g, 0.181 mol, 98%). ^{1}H NMR (300 MHz): 1.33 (s, 3H); 1.34 (s, 3H); 1.70 (s, 3H); 1.75–1.89 (m, 1H); 2.03 (m, 1H); 2.05 (s, 3H); 2.16 (m, 1H); 2.33–2.47 (m, 1H); 3.96 (dd, J_1=11 Hz, J_2=2 Hz, 1H); 4.58 (d, J=7 Hz, 2H); 5.42 (t, J=7 Hz, 1H). To a solution of the resultant (2*E*)-Acetic acid 6-bromo-7-hydroxy-3,7-dimethyl-oct-2-enyl ester (112.00 g, 0.38 mol) in methanol (1 L) at 0 °C was added a solution of NaOH (45.00 g, 1.10 mol) in methanol (350 mL). The reaction mixture was stirred for 1 h at 0 °C, and 3 h at rt. The reaction mixture was concentrated to ca. 100 mL, dissolved in petrol ether (100 mL), washed with water (2×50 mL), dried (Na_2SO_4) and evaporated to give (2*E*)-5-(3,3-Dimethyl-oxiranyl)-3-methyl-pent-2-en-1-ol as pale yellow oil (63.06 g, 0.37 mol, 97%). ^{1}H NMR (300 MHz): 1.26 (s, 3H); 1.30 (s, 3H); 1.62–1.67 (m, 2H); 1.70 (s, 3H); 2.05–2.29 (m, 2H); 2.71 (t, J=6 Hz, 1H); 4.17 (d, J=7 Hz, 2H); 5.42 (t, J=7 Hz, 1H). To a solution of the resultant (2*E*)-5-(3,3-Dimethyl-oxiranyl)-3-methyl-pent-2-en-1-ol (20.00 g, 0.117 mol) in anh. THF (60 mL) at −10 °C under inert atmosphere (N_2) were added a solution of NaH (60%, 6.40 g, 0.160 mol) in anh. THF (120 mL) and neat benzyl bromide (18.62 mL, 0.160 mol) subsequently. The reaction mixture was stirred for 5 h at −10 °C, and 1 h at rt. The reaction mixture was evaporated, dissolved in petrol ether (50 mL), washed with water (2×25 mL) and saturated $NaHCO_3$ (2×25 mL), dried (Na_2SO_4) and evaporated to give the title product as pale yellow oil (29.98 g, 0.115 mol, 98%). IR (film): 2931, 2860, 1717, 1454, 1378, 1274, 1108, 747 cm^{-1}. ^{1}H NMR (300 MHz): 1.26 (s, 3H); 1.30 (s, 3H); 1.60–1.67 (m, 2H); 1.67 (s, 3H); 2.00–2.28 (m, 2H); 2.71 (t, J=6 Hz, 1H); 4.03 (d, J=7 Hz, 2H); 4.51 (s, 2H); 5.42 (t, J=7 Hz, 1H); 7.27–7.37 (m, 5H, Ar). ^{13}C NMR (75 MHz): 16.4 (CH_3), 24.8 (2×CH_3), 27.1 (CH_2), 36.1 (CH_2), 58.3 (C), 63.9 (CH), 66.4 (CH_2), 72.1 (CH_2), 121.3 (CH), 127.5 (CH, Bn), 127.7 (2×CH, Bn), 128.3 (2×CH, Bn), 138.3 (C, Bn), 139.3 (C). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29; Found: C, 78.20; H, 9.31.

4.1.2. (6*E*)-8-Benzyloxy-2,6-dimethyl-octa-1,6-dien-3-ol (9).[14] To a refluxed (120 °C) solution of epoxide **8** (1.00 g, 3.84 mmol) in toluene (10 mL) was added aluminum isopropoxide (0.78 g, 3.84 mmol). The reaction mixture was stirred for 4 h. After cooling to rt, the reaction mixture is treated with 2 N hydrochloric acid (10 mL) in order to decompose the aluminum complex. The organic layer is separated, washed with water (2×25 mL) and saturated $NaHCO_3$ (2×25 mL), dried (Na_2SO_4) and evaporated to give the title product as pale yellow oil (0.95 g, 3.65 mmol, 95%). IR (film): 3468, 2982, 2937, 2860, 1739, 1451, 1375, 1266, 1096, 903, 754 cm^{-1}. ^{1}H NMR (300 MHz): 1.65 (s, 3H); 1.58–1.72 (m, 2H); 1.72 (s, 3H); 1.95–2.15 (m, 2H); 4.03 (d, J=7 Hz, 2H); 4.05 (t, J=7 Hz, 1H); 4.51 (s, 2H); 4.84 (s, 1H); 4.94 (s, 1H); 5.42 (t, J=7 Hz, 1H); 7.27–7.37 (m, 5H, Ar). ^{13}C NMR (75 MHz): 16.4 (CH_3), 17.5 (CH_3), 32.8 (CH_2), 35.4 (CH_2), 66.4 (CH_2), 72.0 (CH_2), 75.5 (CH), 111.7 (C=CH_2), 121.0 (C=CH), 127.4 (CH, Bn), 127.7 (2×CH, Bn), 128.2 (2×CH, Bn), 138.4 (C, Bn), 140.0 (*C*=CH), 147.3 (*C*=CH_2).

4.1.3. (−)-(2′*S*,1*R*,4*E*)-6-Benzyloxy-4-methyl-1-(2′-methyl-oxiranyl)-hex-4-en-1-ol (6). To a solution of racemic alcohol **9** (5.00 g, 20 mmol) in anh. dichloromethane (80 mL) at −10 °C under inert atmosphere (N_2) were added (2*S*,3*S*)-(−)-diisopropyl tartrate (1.35 g, 6.6 mmol), molecular sieves (4 Å, powder activated particle size 5 μm, 4.00 g, 80% w/w of **9**) and titanium tetraisopropylate (1.10 mL, 4 mmol). The reaction mixture was stirred for 0.5 h at −10 °C, cooled down to −30 °C and *tert*-butyl hydroperoxide (TBHP, solution 5.5 M in decane, 1.64 mL, 9 mmol) was added. The reaction mixture was stirred for 6 h at −30 °C until a 1:1 ratio of two spots were observed in TLC. At −30 °C the reaction was quenched by addition of a 5% HCl solution (11 mL),warmed to rt, filtered through a sintered glass and extracted with chloroform (100 mL), washed with water (2×25 mL) and saturated $NaHCO_3$ (2×25 mL), dried (Na_2SO_4) and evaporated. The residue was purified by MPLC (20–50% ethyl acetate–petrol ether [40–60]) to give the unreacted reactant alcohol **6** (2.60 g, 10 mmol, 50%), $[\alpha]_D^{22}$ −4.36 (*c* 2.43, $CHCl_3$) and the title compound as pale yellow oil (2.49 g, 9 mmol, 45%) $[\alpha]_D^{21}$ −2.42 (*c* 1.91, $CHCl_3$). IR (film): 3456, 3356, 2946, 2858, 1663, 1448, 1063, 756 cm^{-1}. ^{1}H NMR (300 MHz): 1.34 (s, 3H); 1.45–1.58 (m, 1H); 1.67 (s, 3H); 1.70–1.83 (m, 1H); 2.09 (s, 1H, ex); 2.09–2.20 (m, 1H); 2.23–2.33 (m, 1H); 2.61 (d, J=5 Hz, 1H); 2.90 (d, J=5 Hz, 1H); 3.63 (dd, J_1=9 Hz, J_2=3 Hz, 1H); 4.04 (d, J=7 Hz, 2H); 4.51 (s, 2H); 5.42 (t, J=7 Hz, 1H); 7.27–7.37 (m, 5H, Ar). ^{13}C NMR (75 MHz): 16.5 (CH_3), 18.0 (CH_3), 30.9 (CH_2), 35.3 (CH_2), 50.2 (CH_2), 58.9 (C), 66.5 (CH_2), 71.2 (CH_2), 72.0 (CH), 121.0 (CH), 127.5 (CH, Bn), 127.7 (2×CH, Bn), 128.3 (2×CH, Bn), 138.4 (C, Bn), 139.9 (C). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.55; H, 8.77. The %ee of hydroxyepoxide **6** was determined by HPLC on Diacel Chiralpack® AD chiral column with 1 mL/min. 96:4 hexane/isopropanol as mobile phase. Retention times for both enantiomers were determined by separation of specially prepared racemic mixture.

4.1.4. (+)-(2*S*,3*R*,6*E*)-(Diethoxy-phosphoryl)-acetic acid-8-benzyloxy-2,3-dihydroxy-2,6-dimethyl-oct-6-enyl ester (10a) and (+)-(2*S*,3*R*,6*E*)-(diethoxy-phosphoryl)-acetic acid-6-benzyloxy-1(1,2-dihydroxy-1-methyl-ethyl)-4-methyl-hex-4-enyl ester (11a). To a solution of hydroxy epoxide **6** (0.0553 g, 0.20 mmol) in anh. dichloromethane (3.0 mL) at rt were added diethylphosphonoacetic acid (0.6 mL solution of 1.0 M, 0.60 mmol) and titanium tetraisopropylate (0.2 mL of 1.0 M solution in dichloromethane, 0.20 mmol). The reaction mixture was stirred for 72 h, filtered through a sintered glass and quenched by a 10% HCl solution (5.0 mL). The reaction mixture was extracted with chloroform (25 mL), washed with water (2×25 mL) and saturated $NaHCO_3$ (2×25 mL), dried (Na_2SO_4) and evaporated. The residue had showed a 2:1 mixture of **10a**:**11a** products according to ^{1}H NMR of crude. The mixture was purified by MPLC (100% ethyl acetate) to give

the pure title compounds **10a** as pale yellow oil (0.0567 g, 0.128 mmol, 64%) and the more polar **11a** as pale yellow oil (0.0331 g, 0.070 mmol, 35%). Compound **10a**: $[\alpha]_D^{23}$ +11.84 (*c* 0.55, $CHCl_3$). IR (film): 3350 (br), 3002, 2935, 2859, 1738, 1451, 1393, 1259, 1158, 1024, 972, 756 cm^{-1}. ^1H NMR (300 MHz): 1.15 (s, 3H); 1.34 (q, $J=7$ Hz, 6H, $P[OCH_2CH_3]_2$); 1.40–1.52 (m, 1H); 1.66 (s, 3H); 1.68–1.82 (m, 1H); 2.05–2.18 (m, 1H); 2.34–2.47 (m, 1H); 2.95 (dd, $J_1=29$ Hz, $J_2=14$ Hz, 1H, CH_2-P); 3.02 (dd, $J_1=30$ Hz, $J_2=14$ Hz, 1H, CH_2-P); 3.26 (d, $J=7$ Hz, 1H, ex); 3.45 (t, $J=9$ Hz, 1H, ex); 3.73 (s, 1H, ex); 3.99 (d, $J=11$ Hz, 1H); 4.02 (d, $J=7$ Hz, 2H); 4.15 (app. sextet, $J=7$ Hz, 2×2H, $P[OCH_2CH_3]_2$); 4.42 (d, $J=11$ Hz, 1H); 4.51 (s, 2H); 5.42 (t, $J=7$ Hz, 1H); 7.20–7.32 (m, 5H, Ar). ^{13}C NMR (75 MHz): 16.2 ($P[OCH_2CH_3]_2$), 16.3 (CH_3), 16.6 (CH_3), 20.7 (CH_2), 29.2 (CH_2-P), 36.7 (CH_2), 63.1 ($P[OCH_2CH_3]_2$), 66.5 (CH_2), 69.9 (CH_2), 72.1 (CH_2), 72.9 (C), 76.1 (CH), 121.1 (C=*C*H), 127.5 (CH, Bn), 127.7 (2× CH, Bn), 128.3 (2×CH, Bn), 138.4 (C, Bn), 140.1 (*C*=CH), 165.5 ($PCH_2C{=}O$). HRMS calcd for $C_{23}H_{37}NaO_8P$ (MNa^+) 495.2124, found 495.2123.

Compound **11a**: $[\alpha]_D^{23}$ +5.41 (*c* 0.44, $CHCl_3$). IR (film): 3402 (br), 2994, 2932, 2862, 1731, 1448, 1395, 1261, 1112, 1029, 974, 752 cm^{-1}. ^1H NMR (300 MHz): 1.10 (s, 3H); 1.35 (t, $J=7$ Hz, 6H, $P[OCH_2CH_3]_2$); 1.64 (s, 3H); 1.65–1.77 (m, 1H); 1.89–2.15 (m, 3H); 2.95 (dd, $J_1=29$ Hz, $J_2=14$ Hz, 1H, CH_2-P); 3.02 (dd, $J_1=30$ Hz, $J_2=14$ Hz, 1H, CH_2-P); 3.32 (d, $J=12$ Hz, 1H); 3.65 (d, $J=12$ Hz, 1H); 4.01 (d, $J=7$ Hz, 2H); 4.17 (app. double sextet, $J=3$ Hz, 2×2H, $P[OCH_2CH_3]_2$); 4.51 (s, 2H); 4.88 (d, $J=9$ Hz, 1H); 5.42 (t, $J=7$ Hz, 1H); 7.20–7.32 (m, 5H, Ar). ^{13}C NMR (75 MHz): 16.2 ($P[OCH_2CH_3]_2$), 16.4 (CH_3), 18.8 (CH_3), 26.6 (CH_2), 29.6 (CH_2-P), 36.2 (CH_2), 63.1 ($P[OCH_2CH_3]_2$), 66.5 (CH_2), 72.1 (CH_2), 73.4 (C), 78.0 (CH), 121.6 (C=*C*H), 127.5 (CH, Bn), 127.7 (2×CH, Bn), 128.3 (2×CH, Bn), 138.4 (C, Bn), 139.1 (*C*=CH), 166.2 ($PCH_2C{=}O$). HRMS calcd for $C_{23}H_{37}NaO_8P$ (MNa^+) 495.2124, found 495.2122.

4.1.5. (+)-(2*S*,3*R*,6*E*)-2,2-Dimethyl-propionic acid 8-benzyloxy-2,3-dihydroxy-2,6-dimethyl-oct-6-enyl ester (10d). To a solution of hydroxyepoxide **6** (2.37 g, 8.58 mmol) in anh. dichloromethane (20 mL) at rt under inert atmosphere (N_2) were added pivalic acid (2.53 g, 24.7 mmol) and titanium tetraisopropylate (3.00 mL, 9.7 mmol). The reaction mixture was stirred overnight (ca. 12 h) at rt. The reaction mixture was quenched by a 5% HCl solution (50 mL), extracted with chloroform (2×100 mL), washed with water (2×25 mL) and saturated $NaHCO_3$ (2× 25 mL), dried (Na_2SO_4) and evaporated to give the title compound as pale yellow oil (2.99 g, 7.89 mmol, 92%). $[\alpha]_D^{21}$ +17.82 (*c* 2.96, $CHCl_3$). IR (film): 2970, 2933, 2862, 1727, 1462, 1369, 1286, 1167, 1073, 931, 742, 689 cm^{-1}. ^1H NMR (300 MHz): 1.17 (s, 3H); 1.22 (s, 9H); 1.40–1.55 (m, 1H); 1.65 (s, 3H); 1.67–1.78 (m, 1H); 2.06–2.17 (m, 1H); 2.27–2.51 (m, 1H+s, 1H, ex); 3.41 (d, $J=8$ Hz, 1H); 4.00 (d, $J=12$ Hz, 1H); 4.02 (d, $J=7$ Hz, 2H); 4.27 (d, $J=$ 12 Hz, 1H); 4.51 (s, 2H); 5.42 (t, $J=7$ Hz, 1H); 7.27–7.37 (m, 5H, Ar). ^{13}C NMR (75 MHz): 16.4 (CH_3), 20.5 (CH_3), 27.2 (3×CH_3, *t*-Bu), 28.8 (CH_2), 36.6 (CH_2), 38.9 (C), 66.4 (CH_2), 68.4 (CH_2), 72.1 (CH_2), 73.9 (C), 75.5 (CH), 121.4 (CH), 127.5 (CH, Bn), 127.7 (2×CH, Bn), 128.3 (2×CH, Bn), 138.4 (C, Bn), 139.9 (C), 178.9 (C=O). HRMS calcd for $C_{22}H_{34}NaO_5$ (MNa^+) 401.2304, found 401.2313.

4.1.6. (−)-(2*S*,6*E*)-8-Benzyloxy-1,2-dihydroxy-2,6-dimethyl-oct-6-en-3-one (12). To a solution of oxalyl chloride (1.20 mL, 13.9 mmol) in anh. dichloromethane (30 mL) at −78 °C under inert atmosphere (N_2) was added dropwise over period of 5 min a solution of DMSO (2.16 mL, 30.4 mmol) in anh. dichloromethane (6 mL). The reaction mixture was stirred for 10 min and a solution of diol **10d** (4.77 g, 12.60 mmol) in anh. dichloromethane (15 mL) was added dropwise over period of 5 min. The reaction mixture was stirred for 30 min and neat triethylamine (8.8 mL, 64.0 mmol) was added dropwise over period of 5 min. The reaction mixture was left to rt and quenched by a 1% HCl solution (40 mL) after TLC analysis showed total disappearance of diol **10d**. The reaction mixture was stirred for additional 10 min and the dimethylsulfide by-product was distilled off (38 °C). The residue was extracted with dichloromethane (2×50 mL), washed with water (2×25 mL) and saturated $NaHCO_3$ (2× 25 mL), dried (Na_2SO_4) and evaporated to give (+)-(2*R*)-(6*E*)-2,2-Dimethyl-propionic acid 8-benzyloxy-2-hydroxy-2,6-dimethyl-3-oxo-oct-6-enyl ester as pale yellow oil (4.41 g, 11.72 mmol, 93%). $[\alpha]_D^{22}$ +6.14 (*c* 1.52, $CHCl_3$). IR (film): 3420 (br), 2937, 2858, 1721, 1651, 1454, 1368, 1283, 1151, 1063, 753 cm^{-1}. ^1H NMR (300 MHz): 1.15 (s, 9H); 1.36 (s, 3H); 1.65 (s, 3H); 2.21–2.46 (m, 2H); 2.69 (t, $J=8$ Hz, 2H); 3.91 (s, 1H, ex); 4.02 (d, $J=7$ Hz, 2H); 4.50 (s, 2H); 5.42 (t, $J=7$ Hz, 1H); 7.27–7.37 (m, 5H, Ar). ^{13}C NMR (75 MHz): 16.4 (CH_3), 20.5 (CH_3), 27.2 (3×CH_3, *t*-Bu), 28.8 (CH_2), 36.6 (CH_2), 38.9 (C), 66.4 (CH_2), 68.4 (CH_2), 72.1 (CH_2), 79.9 (C), 121.6 (C=*C*H), 127.5 (CH, Bn), 127.7 (2×CH, Bn), 128.3 (2×CH, Bn), 138.4 (C, Bn), 138.5 (*C*=CH), 178.0 (C=O, ester) 210.9 (C=O, ketone). To a solution of the resultant (+)-(2*S*,6*E*)-2,2-Dimethyl-propionic acid 8-benzyloxy-2-hydroxy-2,6-dimethyl-3-oxo-oct-6-enyl ester (2.65 g, 7.04 mmol) in methanol (25 mL) at rt was added a solution of NaOH (7.04 mL of 1 N) in methanol. The reaction mixture was stirred for 12 h. at rt, neutralized to pH 6 by a few drops of 1% HCl solution, concentrated to ca.10 mL, dissolved in ethyl acetate (50 mL), washed with water (2×50 mL), dried (Na_2SO_4) and evaporated to give the title product as pale yellow oil (2.00 g, 6.83 mmol, 97%). $[\alpha]_D^{20}$ −0.82 (*c* 0.89, $CHCl_3$). IR (film): 3450 (br), 2923, 2859, 1711, 1452, 1370, 1060, 751 cm^{-1}. ^1H NMR (300 MHz): 1.27 (s, 3H); 1.66 (s, 3H); 2.35 (t, $J=8$ Hz, 2H); 2.72 (t, $J=8$ Hz, 2H); 3.62 (d, $J=$ 12 Hz, 1H); 3.85 (d, $J=12$ Hz, 1H); 4.01 (d, $J=7$ Hz, 2H); 4.50 (s, 2H); 5.42 (t, $J=7$ Hz, 1H); 7.27–7.37 (m, 5H, Ar). ^{13}C NMR (75 MHz): 16.7 (CH_3), 21.3 (CH_3), 32.6 (CH_2), 34.3 (CH_2), 66.4 (CH_2), 67.8 (CH_2), 72.2 (CH_2), 79.6 (C), 121.4 (C=*C*H), 127.6 (CH, Bn), 127.8 (2×CH, Bn), 128.3 (2×CH, Bn), 138.2 (C, Bn), 138.7 (*C*=CH), 212.5 (C=O). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.48; H, 8.23.

4.1.7. (−)-(2*S*,6*E*)-(Diethoxy-phosphoryl)-acetic acid 8-benzyloxy-2-hydroxy-2,6-dimethyl-3-oxo-oct-6-enyl ester (13). To a solution of keto diol **12** (2.70 g, 9.23 mmol) in anh. dichloromethane (35 mL) at rt were added neat diethyl phosphonoacetic acid (1.85 g, 9.23 mmol) and a solution of DCC (2.31 g, 9.23 mmol) in anh. dichloromethane (10 mL).

The reaction mixture was stirred for 30 min, filtered, dissolved in ethyl acetate, washed with saturated $NaHCO_3$ (2×25 mL), dried (Na_2SO_4) and evaporated to give the title product as pale yellow oil (4.04 g, 8.58 mmol, 93%). $[\alpha]_D^{20}$ −4.49 (*c* 0.75, $CHCl_3$). IR (film): 3365, 2924, 1742, 1454, 1259, 1025, 739 cm^{-1}. ^1H NMR (300 MHz): 1.30 (s, 3H); 1.33 (dt, $J_1=7$ Hz, $J_2=0.5$ Hz, 6H, $P[OCH_2CH_3]_2$); 1.66 (s, 3H); 2.27–2.37 (m, 2H); 2.80–3.03 (dd, $J_1=29$ Hz, $J_2=14$ Hz, 1H, CH_2-P+dd, $J_1=30$ Hz, $J_2=14$ Hz, 1H, CH_2-P+m, 2H); 4.02 (d, $J=7$ Hz, 2H); 4.14 (m, 2×2H, $P[OCH_2CH_3]_2$); 4.34 (d, $J=11$ Hz, 1H); 4.38 (d, $J=11$ Hz, 1H); 4.50 (s, 2H); 4.72 (s, 1H, ex); 5.42 (t, $J=7$ Hz, 1H); 7.27–7.37 (m, 5H, Ar). ^{13}C NMR (75 MHz): 16.3 ($P[OCH_2CH_3]_2$), 16.7 (CH_3), 21.8 (CH_3), 32.5 (CH_2), 35.0 (CH_2-P), 35.3 (CH_2), 62.9 ($P[OCH_2CH_3]_2$), 66.4 (CH_2), 69.5 (CH_2), 72.1 (CH_2), 78.3 (C), 121.2 (C=*C*H), 127.5 (CH, Bn), 127.7 (2×CH, Bn), 128.3 (2×CH, Bn), 138.3 (C, Bn), 138.7 (*C*=CH), 165.2 (PCH_2C=*O*), 212.7 (C=O).

4.1.8. (−)-(2*S*,6*E*)-(Diethoxy-phosphoryl)-acetic acid-8-benzyloxy-2-[2-(diethoxy-phosphoryl) -acetoxy]-2,6-dimethyl-3-oxo-oct-6-enyl ester (15). To a solution of **10** (0.05 g, 0.17 mmol) in anh. dichloromethane (10 mL) at rt were added neat diethylphosphonoacetic acid (0.14 g, 0.68 mmol) and a solution of DCC (0.14 g, 0.68 mmol) in anh. dichloromethane (2 mL). The reaction mixture was stirred for 30 min, filtered, dissolved in ethyl acetate, washed with saturated $NaHCO_3$ (2×25 mL), dried (Na_2SO_4) and evaporated to give the title product as pale yellow oil (0.09 g, 0.16 mmol, 95%) after flash chromatography (EtOAc:Methanol, 0–10%). $[\alpha]_D^{21}$ −3.86 (*c* 0.30, $CHCl_3$). IR (film): 2987, 2925, 2857, 1742, 1452, 1376, 1265, 1108, 1026, 966, 753 cm^{-1}. ^1H NMR (300 MHz): 1.33 (dt, $J_1=7$ Hz, $J_2=0.5$ Hz, 12H, 2×$P[OCH_2CH_3]_2$); 1.53 (s, 3H); 1.65 (s, 3H); 2.29 (t, $J=7$ Hz, 2H); 2.67 (t, $J=7$ Hz, 2H); 2.97 (dd, $J_1=29$ Hz, $J_2=14$ Hz, 1H, CH_2-P); 2.98 (d, $J=22$ Hz, 2H); 3.05 (dd, $J_1=30$ Hz, $J_2=14$ Hz, 1H, CH_2-P); 4.15 (quint., $J=7$ Hz, 8H, 2×$P[OCH_2CH_3]_2$); 4.44 (d, $J=12$ Hz, 1H); 4.48 (s, 2H); 4.62 (d, $J=12$ Hz, 1H); 5.42 (t, $J=7$ Hz, 1H); 7.27–7.37 (m, 5H, Ar). ^{13}C NMR (75 MHz): 16.2 2×($P[OCH_2CH_3]_2$), 16.3 (CH_3), 19.1 (CH_3), 22.6 (CH_2), 29.6 2×(CH_2-P), 32.7 (CH_2), 34.8 (CH_2), 66.5 (2×$P[OCH_2CH_3]_2$), 65.8 (CH_2), 72.1 (CH_2), 84.5 (C), 121.1 (C=*C*H), 127.51 (CH, Bn), 127.6 (2×CH, Bn), 128.4 (2×CH, Bn), 137.2 (C, Bn), 138.7 (*C*=CH), 165.3 (2×PCH_2C=*O*), 206.1 (C=O). HRMS calcd for $C_{29}H_{46}NaO_{12}P_2$ (MNa^+) 671.2363, found 671.2328.

4.1.9. (−)-(2*S*,6*E*)-(Diethoxy-phosphoryl)-acetic acid 8-benzyloxy-2,6-dimethyl-3-oxo-2-trimethylsilanyloxy-oct-6-enyl ester (16). To a stirred solution of diethylphosphono acetate ester **14** (2.20 g, 4.68 mmol) in DMF (10 mL) were added 1,1,1,3,3,3-hexamethyldisilazane (2.60 mL, 12.6 mmol) and trimethylsilyl chloride (1.30 mL, 10.3 mmol) at rt. The reaction mixture was stirred for 2 h, dissolved in ethyl acetate, washed with water (2×20 mL) and saturated $NaHCO_3$ (2×25 mL), dried (Na_2SO_4) and evaporated to give the title product as pale yellow oil (2.51 g, 4.63 mmol, 99%). $[\alpha]_D^{20}$ −2.55 (*c* 2.14, $CHCl_3$). IR (film): 2940, 1741, 1651, 1508, 1380, 1262, 1024, 755 cm^{-1}. ^1H NMR (300 MHz): 0.18 (s, 9H, $Si[CH_3]_3$); 1.30 (s, 3H); 1.34 (t, $J=7$ Hz, 6H, $P[OCH_2CH_3]_2$); 1.66 (s, 3H); 2.27 (t, $J=7$ Hz, 2H); 2.78 (t, $J=7$ Hz, 1H); 2.94 (d, $J=22$ Hz, 2H, CH_2-P); 4.02 (d, $J=7$ Hz, 2H); 4.11–4.20 (m, 2×2H, $P[OCH_2CH_3]_2$); 4.25 (d, $J=11$ Hz, 2H); 4.50 (s, 2H); 5.42 (t, $J=7$ Hz, 1H); 7.27–7.37 (m, 5H, Ar). ^{13}C NMR (75 MHz): 1.3 ($Si[CH_3]_3$), 14.3 ($P[OCH_2CH_3]_2$), 16.7 (CH_3), 21.8 (CH_3), 25.8 (CH_2), 31.5 (CH_2), 35.0 (CH_2-P), 62.9 ($P[OCH_2CH_3]_2$), 66.4 (CH_2), 69.5 (CH_2), 72.1 (CH_2), 78.3 (C), 121.2 (C=*C*H), 127.5 (CH, Bn), 127.7 (2×CH, Bn), 128.3 (2×CH, Bn), 138.3 (C, Bn), 138.7 (*C*=CH), 165.3 (PCH_2C=*O*), 212.7 (C=O). HRMS calcd for $C_{23}H_{35}NaO_8P$ (MNa^+ − TMS) 493.1967, found 493.1977.

4.1.10. (+)-(5*R*,3′*E*,3*Z*)-4-(5′-Benzyloxy-3′-methyl-pent-3′-enyl)-5-methyl-5-trimethyl silyloxy-5,6-dihydro-pyran-2-one (17). To a stirred solution of silylated diethylphosphono acetate **16** (0.100 g, 0.18 mmol) in anh. THF (4 mL) under inert atmosphere (N_2) at 0 °C was added a solution of lithium *tert*-butylate in anh. THF (0.4 mL of 0.5 M solution prepared from *tert*-butanol and butyl lithium). The reaction mixture was stirred for 2 h, dissolved in ethyl acetate (20 mL), washed with water (2×20 mL) and saturated $NaHCO_3$ (2×20 mL), dried (Na_2SO_4) and evaporated to give the title product as pale yellow oil (0.063 g, 0.16 mmol, 90%) after flash chromatography (Petrol ether/EtOAc, 8:2→1:1→0:1). $[\alpha]_D^{21}$ +2.30 (*c* 0.89, $CHCl_3$). IR (film): 3013, 2951, 2858, 1729, 1453, 1378, 1251, 1147, 1069, 1020, 850, 755, 697 cm^{-1}. ^1H NMR (300 MHz): 0.16 (s, 9H, $Si[CH_3]_3$); 1.44 (s, 3H); 1.68 (s, 3H); 2.19–2.39 (m+m, 1H+2H); 2.43–2.56 (m, 1H); 4.04 (d, $J=10$ Hz, 1H); 4.07 (d, $J=10$ Hz, 2H); 4.18 (d, $J=10$ Hz, 1H); 4.51 (s, 2H); 5.42 (t, $J=7$ Hz, 1H); 5.66 (s, 1H, lactone); 7.27–7.37 (m, 5H, Ar). ^{13}C NMR (75 MHz): 1.9 ($Si[CH_3]_3$), 16.5 (CH_3), 24.4 (CH_3), 27.8 (CH_2), 36.4 (CH_2), 66.3 (CH_2), 70.8 (C), 72.5 (CH_2), 75.0 (CH_2), 113.6 (C=*C*H, lactone), 121.8 (C=*C*H), 127.5 (CH, Bn), 127.6 (2×CH, Bn), 128.4 (2×CH, Bn), 138.2 (C, Bn), 138.4 (*C*=*CH*), 163.6 (*C*=*CH*, lactone), 167.0 (C=O). Anal. Calcd for $C_{22}H_{32}O_4Si$: C, 68.00; H, 8.30. Found: C, 67.66; H, 8.31.

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References and notes

1. (a) Hara, M.; Takahashi, I.; Yoshida, M.; Asano, K.; Kawamoto, I.; Morimoto, M.; Nakano, H. *J. Antibiot.* **1989**, *42*, 333–335. (b) Hara, M.; Saitoh, Y.; Nakano, H. *Biochemistry* **1990**, *29*, 5676–5681.
2. Hara, M.; Asano, K.; Kawamoto, I.; Takiguchi, T.; Katumata, S.; Takahashi, K.; Nakano, H. *J. Antibiot.* **1989**, *42*, 1768–1774.
3. Asai, A.; Hara, M.; Kakita, S.; Kanda, Y.; Yoshida, M.; Saito, H.; Saitoh, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6802–6803.
4. Mitra, K.; Kim, W.; Daniels, J. S.; Gates, K. S. *J. Am. Chem. Soc.* **1997**, *119*, 11691–11692.
5. Breydo, L.; Zang, H.; Gates, K. S. *Tetrahedron Lett.* **2004**, *45*, 5711–5716.

6. Kanda, Y.; Ashizawa, T.; Kakita, S.; Takahashi, Y.; Kono, M.; Yoshida, M.; Saitoh, Y.; Okabe, M. *J. Med. Chem.* **1999**, *42*, 1330–1332.
7. Denny, W. A. *Curr. Med. Chem.* **2001**, *8*, 533–544.
8. Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451–8452.
9. (a) Chatterji, T.; Kizil, M.; Keerthi, K.; Chowdhury, G.; Pospísil, T.; Gates, K. S. *J. Am. Chem. Soc.* **1997**, *119*, 11691–11692. (b) Lee, A. H. F.; Chen, J.; Chan, A. S. C.; Li, T. *Phosphorus, Sulfur Siliicon Relat. Elem.* **2003**, *178*, 1163–1174. (c) Salvetti, R.; Martinetti, G.; Ubiali, D.; Pregnolato, M.; Pagani, G. *Farmaco* **2003**, *58*, 995–998.
10. Kodama, M.; Minami, H.; Mima, Y.; Fukuyama, Y. *Tetrahedron Lett.* **1990**, *31*, 4025–4026.
11. Poppe, L.; Novák, L.; Kolonits, P.; Bata, A.; Szántay, C. *Tetrahedron* **1988**, *44*, 1477–1487.
12. Liao, X.; Xu, X. *Tetrahedron Lett.* **2000**, *41*, 4641–4644.
13. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5165–5180.
14. Terao, S.; Shirashi, M.; Kato, K. *Synthesis* **1979**, 467–468.
15. Chiral racemic and non-racemic compounds are identified by *R*/*S* names only according to Sharpless oxidation product.
16. Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560–1563.
17. For example: McDonald, F. E.; Reddy, K. B.; Díaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304–4309.
18. (a) Seebach, D.; Hungerbuehler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zueger, M. *Synthesis* **1982**, 138. (b) Seebach, D.; Weidmann, B.; Widler, L. In *Modern synthetic methods*; Scheffold, R., Ed.; Sauerlaender: Aarau, 1983; p 217.
19. Momose, T.; Setoguchi, M.; Fujita, T.; Tamura, H.; Chida, N. *Chem. Commun.* **2000**, 2237–2238.
20. Falb, E.; Yechezkel, T.; Salitra, Y.; Gilon, C. *J. Pept. Res.* **1999**, *53*, 507–517.
21. Nahmany, M.; Melman, A. *Org. Lett.* **2001**, *3*, 3733–3735.
22. Weihe, G. R.; Mcmorris, T. C. *J. Org. Chem.* **1978**, *43*, 3942.
23. Lehmann, H.-G.; Weichert, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 300–301.
24. Nangia, A.; Bheema, R. P. *Tetrahedron Lett.* **1992**, *33*, 2375–2378.
25. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.