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STUDIES TOWARD UNIQUE MYCOLACTONE MACROLIDES FROM *MYCOBACTERIUM ULCERANS*

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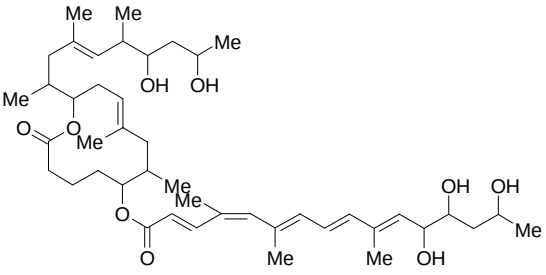
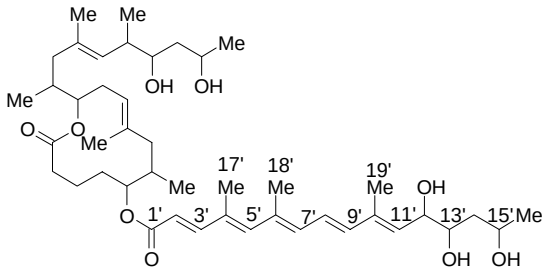
Abstract - The synthesis of C1′- C19′ segments of mycolactones A and B with well defined stereochemical centers at C-12′, C-13′ and C-15′ has been described.

INTRODUCTION

Buruli Ulcer (BU) is a rapidly emerging health hazard and is referred to as the modern leprosy.[1] *Mycobacterium (M.) ulcerans*, the causative agent of BU, is a unique extracellular pathogen of mycobacteria because of the fact that its pathology appears to be mediated by toxin production. There is neither a detection tool, nor an effective drug, or vaccine that could prevent the spread of *M. ulcerans*. However, a major breakthrough has been reported [2,3] by Small *et al.* when two mycolactones A and B (**1** and **2**) of polyketide backbone, were isolated from the toxin. This discovery, constituting the first identification[4] of macrolide produced by a human pathogen as well as the only macrolide identified in mycobacteria, appears to be of paramount significance because of increasing incidences of mycobacterial diseases particularly in HIV infected patients.[5]



Mycolactone A (1)



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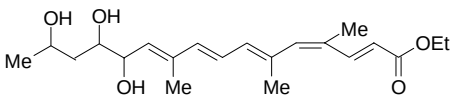

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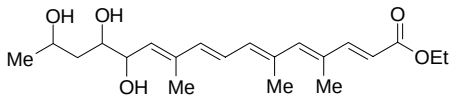

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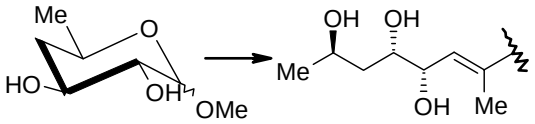
Compounds (**1**) and (**2**) differ in configuration[6] of olefin at C-4′. In an effort to design a versatile approach towards **1** and **2**, we first embarked on the synthesis of C1′-C19′ segments (**3** and **4**) of **1** and **2** starting from 4,6-dideoxyhexoses. The concept of our synthetic design was based on the fact that stereochemical centers at C-12, C-13 and C-15 of **3** and **4** could be correlated to C-2, C-3 and C-5 of 4,6-dideoxyhexoses. For

instance, (12*S*, 13*S*, 15*R*) configuration of **3** and **4** would result from 4,6-dideoxy-D-glucose and likewise, (12*R*,13*S*, 15*R*), (12*S*, 13*R*, 15*R*), and (12*R*, 13*R*, 15*R*) configuration from D-mannose, D-allose and D-



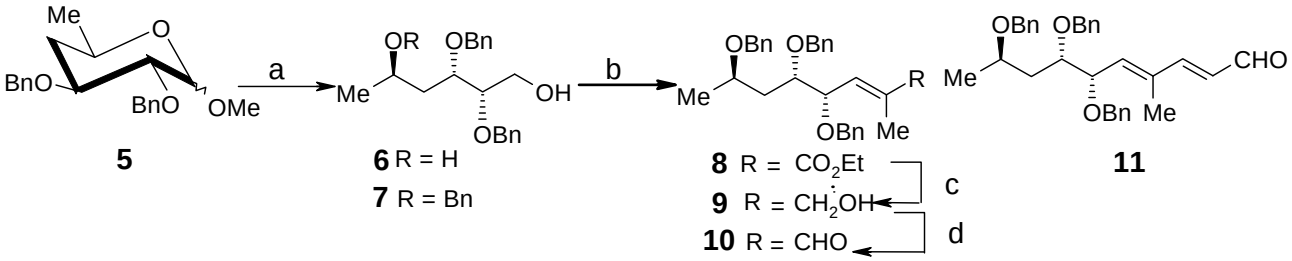
methyl 4,6-dideoxy-D-glucose (12*S*, 13*S*, 15*R*)

altrose derivatives respectively. This paper reports a strategy to construct the highly olefinated side chain at C-1 position of 4,6-dideoxyhexose with well defined stereochemistry and more importantly opens an avenue to easily access the other diastereomers of **3** and **4**.

RESULTS AND DISCUSSION

Successive hydrolysis of methyl glycoside bond in (**5**)[7,8] in presence of H_2SO_4 in dioxane-water in boiling water bath followed by reduction with $NaBH_4$-MeOH afforded the diol (**6**) (**Scheme 1**). By adopting protection–deprotection technique, **6** was transformed into the alcohol (**7**) whose Swern oxidation and

Scheme 1



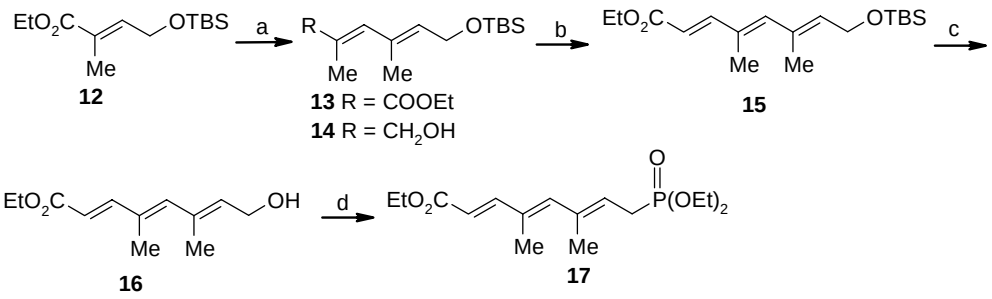
a) (i) H_2SO_4, dioxane-water, 100 ^oC, 12 h; (ii) $NaBH_4$, MeOH, 0.5 h, 54 % (over two steps); (iii) TBSCl, imidazole, CH_2Cl_2, 2 h; (iv) BnBr, NaH, DMF, 2 h; (v) 1M n-Bu_4NF in THF, 0.5 h, 75 % (over three steps); b) (i) $(COCl)_2$, DMSO, Et_3N, -78 ^oC, 1 h; (ii) $Ph_3P{=}C(Me)CO_2Et$, C_6H_6, reflux, 3 h, 80 %; c) DIBAL-H, CH_2Cl_2, -78 ^oC, 0.5 h, 94 %; d) MnO_2, $CHCl_3$, 3 h, rt.

Wittig reaction with $Ph_3P{=}C(Me)CO_2Et$ in refluxing benzene gave (*E*)-unsaturated ester (**8**). Subsequent reduction of **8** with DIBAL-H in CH_2Cl_2 at –78 ^oC gave the alcohol (**9**) which was oxidized with MnO_2 in $CHCl_3$ at room temperature to give the aldehyde (**10**). The iterative approach of sequential Wittig, reduction and oxidation on **10** to build the polyene backbone was hampered due to poor stability of the aldehyde (**11**).

By iterative approach involving reduction, oxidation and Wittig olefination, compound (**12**) was

transformed into the triene derivative (**15**) *via* compounds (**13**) and (**14**) (**Scheme 2**). The TBS group was cleaved (1M Bu_4NF in THF) from **15** and bromine was introduced at the hydroxyl center using PBr_3 in ether at 0 °C and treated with neat triethyl phosphite at 90 °C for 6 h to give the phosphonate (**17**). The ^{1}H- and ^{13}C-NMR spectra of **17** were in agreement with the assigned structure. Condensation of **17** with **10**

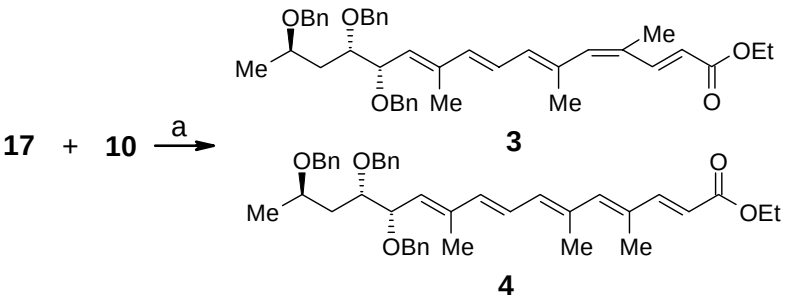
Scheme 2



a) (i) DIBAL-H, CH_2Cl_2 - 78 °C, 0.5 h; (ii) MnO_2, $CHCl_3$, rt, 3 h; (iii) Ph_3P=CMeCOOEt, C_6H_6, reflux, 3 h, 84 % (over two steps); (iv) DIBAL-H, CH_2Cl_2, - 78 °C, 0.5 h, 92 %; b) (i) MnO_2, $CHCl_3$, rt, 4 h; (ii) Ph_3P=$CHCO_2Et$, C_6H_6, reflux, 1.5 h, 83 %; c) 1M *n*-Bu_4NF in THF, 1 h, 93 %; d) PBr_3, Et_2O, 0 °C, 4 h, (ii) $P(OEt)_3$, 90 °C, 6 h, 64 % (over two steps).

was carried out in presence of LDA in THF at –78 °C to 0 °C **(Scheme 3)**. The TLC homogeneous product was isolated whose ^{1}H- and ^{13}C-NMR spectra showed the presence of *cis* (**3**) and *trans* (**4**) isomers in 3:2 ratio. The baseline separation on HPLC of *cis* (slower moving) and *trans* (faster moving) isomers was conveniently carried out on chiral column (Chiralcel OD) with 5% isopropanol in n-hexane as eluent. The individual fractions containing *cis* and *trans* isomers were concentrated. Their HPLC analysis confirmed that a dynamic equilibrium exists between the two isomers as the fraction containing *cis* isomer (**3**) was found to be contaminated with the *trans* isomer (**4**) (12 %) and *vice-versa*.

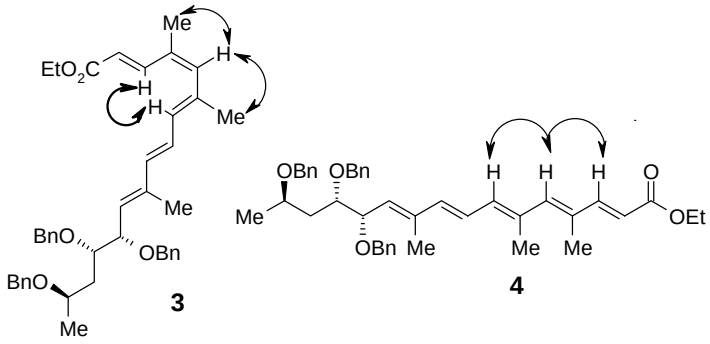
Scheme 3



a) LDA, THF, -78 ° to 0 °C, 1 h, 65 %.

The ^{1}H- and ^{13}C-NMR data of fractions enriched with compounds (**3**) and (**4**) were compared with those

available for naturally occurring mycolactones A and B and this indeed was very much helpful in assigning the correct stereochemistry of both the products. For instance, the ^{1}H NMR spectrum of the *trans* isomer (**4)** showed characteristic doublets at δ 7.40 (J = 16.0 Hz) and δ 6.29 (J = 10.6 Hz) for H-3 and H-7 respectively. The corresponding signals in the *cis* isomer (**3)** appeared at δ 7.96 (d, J = 15.5 Hz) and δ 6.15 (d, J = 11.1 Hz). These values correspond well with those reported for natural products. In the ^{13}C-NMR spectrum of **4**, C-3 was observed at δ 150.0 and for compound (**3**), at 142.5 ppm. The 2D-NOESY studies were also carried out for **3** and **4**. Interestingly, H-5 in compound **3** appeared at δ 6.27



NOE signals of 3 and 4

showed NOE with 17-CH_3 and 18-CH_3as expected. The NOE of H-3 (δ 7.96) with H-7 (δ 6.15) and H-5 was observed. However, in the *trans* isomer (**4**), the NOE of H-5 (δ 6.39) with both H-3 (δ 7.40) and H-7 (δ 6.29) suggested the *E*-configuration at C-4. The lack of NOEs between H-3 (δ 7.40) and H-7 (δ 6.29) was also noticed.

In conclusion, a versatile synthetic strategy to build stereochemically well defined C1'-C19' segments of mycolactones A and B has been accomplished.

EXPERIMENTAL

The NMR spectra were recorded on Bruker AC 200, MSL 300 and DRX-500 MHz machines using $CDCl_3$ as a solvent and TMS as an internal standard. Microanalysis was carried on Carlo-Elba elemental analyser model 1108EA. Optical roatations were measured on JASCO DIP 1020 digital polarimeter. Silica gel (60-120 mesh) was purchased from Acme Chemical Company. Tlc was run on E Merck pre-coated silica gel plates of 0.25 mm thickness. Solvents were dried as per literature procedures and light petroleum refers to mixture of hexanes, bp 60-80 ^{0}C.

(2*S*,3*S*,5*R*)-2,3-Dibenzyloxyhexane-1,5-diol (**6**)

Compound (**5**) (3.5 g, 10.2 mmol) and conc. H_2SO_4 (1 mL) in 2:1 dioxane-water mixture (20 mL) were heated on boiling water bath for 12 h. The reaction mixture was neutralized with solids $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to afford a residue (2.0 g) which was dissolved in methanol (10 mL) and $NaBH_4$ (0.5 g, 13 mmol) was added at 0 ^oC. After 0.5 h, excess of $NaBH_4$ was decomposed with acetic acid, solvent removed and solution extracted with $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. The crude product was purified on silica gel with light petroleum-EtOAc (7:3) as eluent to give **6** (1.82 g, 54 %) as a syrup. $[\alpha]_D$ -30.2^o (c 1.0, $CHCl_3$). ^{1}H NMR (200 MHz): δ 1.20 (d, 3 H, J = 6.6 Hz), 1.65 (m, 2 H), 2.30 (br s, 2 H), 3.5-4.0 (m, 5 H), 4.65 (m, 4 H), 7.25 (m, 10 H); ^{13}C NMR (50 MHz): 24.04, 39.48, 61.20, 64.33, 72.53, 73.00, 76.20, 80.83, 127.48-128.18, 138.25. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.72; H, 7.87. Found: C, 72.83; H, 7.79.

(2*S*,3*S*,5*R*)-2,3,5-Tribenzyloxyhexan-1-ol (7)

A solution of **6** (1.1 g, 3.3 mmol), imidazole (0.25 g, 3.6 mmol) and TBSCl (0.55 g, 3.6 mmol) in CH_2Cl_2 (10 mL) under nitrogen was stirred at rt for 2 h. It was washed with water, dried (Na_2SO_4) and evaporated. To the resulting product in DMF (5 mL) was added NaH (50 % dispersion in oil, 0.32 g, 6.7 mmol). After 15 min, benzyl bromide (1.2 mL, 6.5 mmol) was introduced and further stirred for at rt 2 h. Water was added to the reaction, extracted with Et_2O and washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was dissolved in THF (10 mL) and then 1M solution of Bu_4NF in THF (3 mL) was added and stirred at rt for 0.5 h. Removal of the solvent followed by silica gel chromatography with light petroleum-EtOAc (9:1) as eluent gave **7** (1.05 g, 75 %) as a syrup. $[\alpha]_D$ - 49.6^o (c, 0.7, $CHCl_3$). ^{1}H NMR (200 MHz): δ 1.30 (d, 3 H, J = 6.6 Hz), 1.5-1.65 (m, 2 H), 2.40 (br s, 1 H), 3.6-3.75 (m, 4 H), 3.8-4.0 (m, 1 H), 4.2-4.4 (m, 2 H), 4.55-4.7 (m, 4 H), 7.26 (m, 15 H); ^{13}C NMR (50 MHz): δ 19.85, 38.16, 61.43, 69.84, 71.31, 72.34, 72.67, 75.21, 79.88, 127.2-128.8, 138.36 (2C),138.91. MS (m/z): 420 (M^+).

Ethyl (2*E*,4*S*,5*S*,7*R*)-4,5,7-Tribenzyloxy-2-methylocten-2-oate (8)

To a stirred solution of DMSO (1.2 mL, 1.7 mmol) and oxalyl chloride (0.7 mL, 8.0 mmol) in CH_2Cl_2 (10 mL) at - 78 ^oC, compound **7** (1.5 g, 3.6 mmol) in CH_2Cl_2 (2 mL) was added. After 1 h at – 78 ^0C, Et_3N (2.2 mL) was added and then allowed to attain rt. The reaction mixture was extracted with CH_2Cl_2, washed with water, dried (Na_2SO_4) and concentrated. The resulting aldehyde (1.4 g) and Ph_3P=CMeCOOEt (2.6 g, 7.0 mmol) in benzene (15 mL) were heated under reflux for 3 h. Solvent was evaporated and residue was purified on silica gel with light petroleum-EtOAc (20:1) to afford **8** (1.35 g,

80 %) as a syrup. $[\alpha]_D$ –37.5^o (c 1.0, $CHCl_3$). ^{1}H NMR (200 MHz): δ 1.20 (d, 3 H, J = 6.6 Hz), 1.30 (t, 3 H, J = 6.6 Hz), 1.5-1.8 (m, 2 H), 1.85 (s, 3 H), 3.75 (m, 1 H), 3.90 (m, 1 H), 4.25 (m, 4 H), 4.36 (d, 2 H, J= 13.3 Hz), 4.56 (d, 1H, J = 13.3), 4.63 (d, 1H, J = 13.3 Hz), 4.73 (d, 1 H, J = 13.3 Hz), 6.70 (d, 1 H, J = 10.0 Hz), 7.25 (m, 15 H); ^{13}C NMR (50 MHz): δ 13.10, 14.01, 19.67, 38.93, 60.43, 69.84, 70.65, 71.06, 73.59, 77.75, 127.19-128.0, 131.49, 138.43, 138.69, 138.80, 166.92. Anal. Calcd for $C_{32}H_{38}O_5$: C, 76.49; H, 7.56. Found: C, 76.86; H, 7.69.

(2*E*,4*S*,5*S*,7*R*)-4,5,7-Tribenzyloxy-2-methyl-2-octen-1-ol (9)

A solution of **8** (0.12 g, 0.24 mmol) and DIBAL (1 M solution in toluene, 0.5 mL, 0.5 mmol) in CH_2Cl_2 (10 mL) at –78 ^{o}C was stirred at –78 ^{o}C for 30 min and then decomposed by adding saturated aqueous solution of sodium potassium tartrate. The reaction was extracted with CH_2Cl_2, washed with water and dried (Na_2SO_4). Evaporation of the solvent followed by silica gel column chromatography (light petroleum-EtOAc, 5:1) afforded **9** (0.10 g, 94 %) as a syrup. $[\alpha]_D$ –36^o (c 1, $CHCl_3$); ^{1}H NMR (200 MHz): δ 1.19 (d, 3 H, J = 6.4 Hz), 1.61 (m, 2H), 1.65 (s, 3 H), 1.90 (br s, 1 H), 3.77 (m, 2H), 4.00 (s, 2 H), 4.19 (m, 1 H), 4.25-4.8 (m, 6 H), 5.40 (d, 1 H, J = 9.7 Hz), 7.25 (m, 15 H); ^{13}C NMR (75 MHz): 14.31, 19.83, 39.25, 67.60, 70.10, 71.48, 73.70, 77.85, 78.34, 122.63, 127.57-128.06, 138.80, 140.51. Anal. Calcd for $C_{30}H_{36}O_4$: C, 78.26; H, 7.82. Found: C, 78.49; H, 7.61.

(2*E*,4*S*,5*S*,7*R*)-4,5,7-Tribenzyloxy-2-methyl-2-octenal (10)

Compound **9** (0.20 g, 0.43 mmol) and freshly prepared MnO_2 (0.20 g, 2.3 mmol) in $CHCl_3$ (5 mL) were stirred at rt for 3 h, filtered and concentrated to get the aldehyde **10** (0.19 g) [^{1}H NMR (200 MHz): δ 1.20 (d, 3 H, J = 6.1 Hz), 1.65 (s, 3H), 1.50-1.80 (m, 2 H), 3.65-4.0 (m, 2 H), 4.19 (d, 1H, J = 11.5 Hz), 4.25-4.75 (m, 6 H), 6.40 (d, 1 H, J = 7.7 Hz), 7.24 (m, 15 H), 9.45 (s, 1 H)] which being unstable was used as such for the next reaction.

Ethyl (2*E*,4*E*)-6-*tert*-Butyldimethylsiloxy-2,4-dimethyl-2,4-hexadienoate (13)

Compound (**12**)[9] (1.0 g, 3.9 mmol) was reduced with DIBAL (1 M solution in toluene, 8.5 mL, 8.5 mmol) at – 78 ^{0}C and processed as indicated above. Oxidation of the resulting product (0.77 g) with MnO_2 (1.5 g, 18 mmol) in $CHCl_3$ followed by Wittig reaction with Ph_3P=CMeCOOEt (2.0 g, 5.3 mmol) in refluxing benzene for 3 h and usual work up gave gave **13** (0.89 g, 84 %) as a syrup. ^{1}H NMR (200 MHz): δ 0.20 (s, 6 H), 0.86 (s, 9 H), 1.25 (t, 3 H, J = 7.1 Hz), 1.75 (s, 3 H), 1.94 (s, 3 H), 4.20 (q, 2 H, J = 7.1 Hz), 4.30 (d, 2 H, J = 5.4 Hz), 5.70 (t, 1H, J = 5.4 Hz), 7.11 (s, 1 H). ^{13}C NMR (50 MHz): -5.47, 13.60, 14.01, 16.30, 18.0, 25.60, 59.90, 60.20, 126.0, 132.0, 134.40, 141.50, 168.0. Anal. Calcd for $C_{16}H_{30}O_3Si$: C, 64.43; H, 10.06. Found: C, 64.08; H, 10.25.

Ethyl (2*E*,4*E*,6*E*)-8-*tert*-Butyldimethylsilyloxy-4,6-dimethyl-2,4,6-octatrienoate (15)

Compound **13** (1.2 g, 4.02 mol) was reduced with DIBAL (1 M solution in toluene, 9.3 mL, 9.3 mmol) as reported above to give **14** (0.95 g, 92 %). ^{1}H NMR (200 MHz): δ 0.1 (s, 6 H), 0.84 (s, 9 H), 1.69 (s, 3 H), 1.74 (s, 3 H), 4.0 (s, 2 H), 4.25 (d, 2 H, J = 6.2 Hz), 5.43 (t, 1 H, J = 6.15 Hz), 5.86 (s, 1 H). ^{13}C NMR (50 MHz): δ -5.40, 14.90, 16.80, 17.98, 25.62, 59.92, 68.19, 127.70, 128.99, 132.81, 135.24. Oxidation of **14** (1.1 g, 4.3 mmol) with MnO_2 (1.8 g, 21.5 mmol) in $CHCl_3$ (25 mL) as reported above, gave the aldehyde which was treated with Ph_3P=CHCOOEt (2.2 g, 6.2 mmol) in refluxing benzene (7 mL) for 1.5 h followed by usual work up and silica gel chromatography (light petroleum-EtOAc, 9:1) gave **15** (1.14 g, 83 %) as a syrup. ^{1}H NMR (200 MHz): δ 0.10 (s, 6 H), 0.82 (s, 9 H), 1.21 (t, 3 H, J = 7.5 Hz), 1.73 (s, 3 H), 1.87 (s, 3 H), 4.10 (q, 2 H, J = 7.5 Hz), 4.25 (d, 2 H, J = 6.8 Hz), 5.52 (t, 1 H, J = 6.8 Hz), 5.74 (d, 1 H, J = 15.3 Hz), 6.15 (s, 1 H), 7.24 (d, 1 H, J = 15.3 Hz); ^{13}C NMR (50 MHz): δ -5.50, 13.30, 14.0, 16.62, 17.94, 25.55, 59.60, 59.80, 116.67, 131.96, 132.40, 133.40, 141.89, 149.68, 166.63. Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.60; H, 9.87. Found: C, 66.54; H, 9.97.

Ethyl (2*E*,4*E*,6*E*)-8-Diethoxyphosphinyl-4,6-dimethyl-2,4,6-octatrienoate (17)

A solution of **15** (0.3 g, 0.92 mmol) and 1M solution of Bu_4NF (1.38 mL, 1.38 mmol) in THF (2 mL) was stirred at rt for 1 h and evaporated. The residue was purified on silica gel with light petroleum-EtOAc (7:3) as eluent to give **16** (0.18 g, 93 %) as a syrup. ^{1}H NMR (200 MHz): δ 1.31 (t, 3 H, J = 6.25 Hz), 1.85 (s, 3 H), 1.97 (s, 3 H), 4.15 (q, 2 H, J = 6.25 Hz), 4.25 (d, 2 H, J = 6.0 Hz), 5.70 (t, 1 H, J = 6.0 Hz), 5.85 (d, 1 H, J = 15.6 Hz), 6.22 (s, 1 H), 7.31 (d, 1H, J = 15.6). A solution of **16** (0.6 g, 2.9 mmol) and PBr_3 (0.1 mL, 1.15 mmol) in ether (5 mL) was stirred at 0 ^{0}C for 4 h. The reaction mixture was quenched by the addition of saturated aqueous solution of KBr and layers separated. The aqueous layer was extracted with ether. The combined organic layer was washed with water, dried (Na_2SO_4) and evaporated. The resulting product and triethyl phosphite (0.4 mL, 2.43 mmol) were heated at 90 ^{o}C for 6 h and chromatographed on silica gel with light petroleum-EtOAc (2:3) as eluent to give **17** (0.60 g, 64 %) as a syrup. ^{1}H NMR (200 MHz): δ 1.2 (m, 9 H), 1.80 (d, 3 H, J = 4.5 Hz), 1.90 (s, 3 H), 2.65 (dd, 2 H, J = 8.6, 22.8 Hz), 4.10 (m, 6 H), 5.40 (q, 1 H, J = 8.6, 14.3 Hz), 5.80 (d, 1 H, J = 16.9 Hz), 6.20 (s, 1 H), 7.25 (d, 1 H, J = 16.9 Hz). Anal. Calcd for $C_{16}H_{27}O_5P$: C, 58.18; H, 8.18. Found: C, 58.43; H, 8.16.

Ethyl (2*E*,4*Z*,6*E*,8*E*,10*E*,12*S*,13*S*,15*R*)-12,13,15-Tribenzyloxy-4,6,10-trimethyl-2,4,6,8,10-hexadecapentaenoate (3) and Ethyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*R*)-12,13,15-Tribenzyloxy-4,6,10-trimethyl-2,4,6,8,10-hexadecapentaenoate (4).

To the freshly prepared solution of LDA (from 0.5 mL of 2 M n-BuLi and 0.1 mL of diisopropylamine) at –78 ^{o}C, compounds (**17**) (0.40 g, 1.2 mmol) and (**10**) (0.28 g, 0.62 mmol) were added. The reaction

mixture was allowed to attain 0 ^{o}C over a period of 1 h, quenched with saturated NH_4Cl solution and layers separated. The aqueous layer was extracted with $CHCl_3$, washed with water, dried (Na_2SO_4) and concentrated. The residue was purified on silica get with light petroleum - EtOAc (9:1) as eluent to afford the mixture of diastereomers (**3** and **4**) (0.25 g, 65 %) .The chiral HPLC separation (on Chiralcel OD column with 5 % isopropanol in hexane as eluent, UV = 254 nm, flow rate = 1 mL/min) gave the 4*E*-isomer (**4**) (retention time = 12.5 min). $[\alpha]_D$ + 57^{o} (c 0.8, $CHCl_3$). ^{1}H NMR (500 MHz): δ 1.21 (d, 3 H, J = 6.1 Hz), 1.34 (t, 3 H, J = 7.1 Hz), 1.55 (ddd, 1 H, J = 2.5, 9.2, 13.3 Hz), 1.72 (ddd, 1 H, J = 2.0, 9.2, 13.3 Hz), 1.84 (d, 3 H, J = 0.5 Hz), 3.79 (m, 1 H), 3.88 (m, 1 H), 4.25 (q, 2 H, J = 7.1 Hz), 4.27 (d, 1 H, J = 10.9 Hz), 4.34 (dd, 1 H, J = 6.5, 9.8 H z), 4.40 (d, 1H, J = 10.9 Hz), 4.43 (d, 1 H, J = 10.9 Hz), 4.57 (d, 1 H, J = 10.9 Hz), 4.62 (d, 1 H, J = 10.9 Hz), 4.85 (d, 1 H, J = 10.9 Hz), 5.58 (d, 1 H, J = 10.6 Hz), 5.90 (d, 1 H, J = 16.0 Hz), 6.29 (d, 1 H, J = 10.6 Hz), 6.39 (s, 1 H), 6.42 (d, 1 H, J = 16.0 Hz), 6.56 (dd, 1 H, J = 10.6, 16.0 Hz), 7.3 (m, 15 H), 7.40 (d, 1 H, J = 16.0 Hz); ^{13}C NMR (125 MHz): 13.05, 13.92, 14.07, 16.64, 19.64, 39.34, 54.93, 69.95, 70.04, 71.09, 73.92, 78.33, 78.39, 116.09, 124.22, 127.18-128.02, 131.00, 134.43, 138.59-138.66, 143.23, 150.0, 167.3. Anal. Calcd for $C_{42}H_{50}O_5$: C, 79.49; H, 7.88. Found: C, 79.11; H, 7.71.

The second fraction eluted was the 4*Z*-isomer (**3**) (retention time = 19.4 min.). $[\alpha]_D$ + 55.4^{o} (c 0.7, $CHCl_3$). ^{1}H NMR (500 MHz): δ 1.21 (d, 3 H, J = 6.0 Hz), 1.32 (t, 3 H, J = 7.1 Hz), 1.55 (ddd, 1 H, J = 2.5, 10.1, 13.2 Hz), 1.73 (ddd, 1 H, J = 2.0, 10.1, 13.1 Hz), 1.83 (d, 3 H, J = 0.5 Hz), 1.98 (d, 3 H, J = 0.5 Hz), 2.04 (s, 3 H), 3.79 (m 1 H), 3.89 (m, 1 H), 4.20 (q, 2 H, J = 7.1 Hz), 4.27 (d, 1 H, J = 10.1 Hz), 4.33 (dd, 1 H, J = 6.7, 10.1 Hz), 4.40 (d, 1 H, J = 11.3 Hz), 4.44 (d, 1H, J = 10.7), 4.57 (d, 1H, J = 10.7 Hz), 4.62 (d, 1 H, J = 11.3 Hz), 4.84 (d, 1 H, J = 10.7 Hz), 5.55 (d, 1 H, J = 11.1 Hz), 5.95 (d, 1 H, J = 15.5 Hz), 6.15 (d, 1 H, J = 11.1 Hz), 6.27 (s, 1 H), 6.40 (dd, 1 H, J = 11.1, 15.5 Hz), 7.3 (m, 15 H), 7.96 (d, 1 H, J = 15.5 Hz); ^{13}C NMR (125 MHz): 13.0, 13.99, 17.18, 19.65, 20.69, 39.30, 59.87, 69.89, 70.04, 71.21, 73.75, 78.33, 78.43, 118.24, 124.27, 127.09-127.95, 130.68, 133.59, 138.11-138.78, 140.87, 142.50, 167.23. MS: *m/z* 634 (M^+). Anal. Cacd for $C_{42}H_{50}O_5$: C, 79.49; H, 7.88. Found: C, 79.28; H, 8.01.

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