Stereoselective Synthesis of C1-C6 and C7-C22 Fragments of (-) Callystatin A

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Received: September 05, 2015
Accepted: October 15, 2015
Published: October 21, 2015


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Introduction

Callystatin A, biologically potent marine natural product with intricate structural features are always attractive synthetic targets to organic chemists. Natural products of marine origin are generally obtained in minute quantities (1 mg from 10 kg of sponge from callyspongia truncate [1]) that are insufficient for detailed biological activity studies. In 1997 Kobayashi and co-workers disclosed the isolation and planar structure of (-) callystatin A [1], a remarkably potent cytotoxic agent (e.g. IC50 0.01 ng/mL in vitro against the KB cancer cell line). Kobayashi group determined the absolute configuration of the (-)-callystatin A via partial [2] and total synthesis [3] by preparing several structural analogues, which led to further insight on structure-activity relationships [4]. The structure of (-)-callystatin A contains a polypropionate chain and a lactone ring connected to each other by two conjugated diene systems separated by two sp³ hybridised carbon atoms.

Abstract

The stereoselective synthesis of the two major fragments (C1-C6 and C7-C22) of cytotoxic polyketide marine natural product (-)-callystatin A, has been achieved with Sharpless epoxidation, desymmetrization strategy, Horner-Wadsworth-Emmons reaction and witting olefination.

Keywords: (-)-Callystatin A; Desymmetrization; Horner-Wadsworth-Emmons reaction.

Results and Discussion

We devised a general retrosynthetic strategy that leads to three building blocks of comparable molecular complexity (Scheme 1).

In this paper, we report scalable synthesis of the C1-C6 fragment 2 from 3-butyne-1-ol, C7-C12 fragment 5 from (S)-Roche ester and C13-C22 fragment 6 from a bicyclic olefin 10 using desymmetrization strategy. We achieved the fragment (C7-C22) using the convergent approach joining the two subunits (5 and 6) together with Wittig olefination. Preliminary results were published recently as a communication [5]. In literature the formation of C13-C22 propionate fragment was to be constructed through convergent synthesis with expensive reagents [6-8]. The formation methyl chiral substrates is very difficult with appropriate configuration. In this study, we have employed the desymmetrization strategy with linear protocol.
The synthesis of the C₁-C₆ fragment (2) based on sequence of reactions starting from the commercial available compound 3-butyne-1-ol 7. The compound 7 was protected as its p-methoxy benzy alcohol using PMBBr and NaH in dry THF at room temperature to afford the compound 11 in 81% yield [9]. The compound 11 was treated with the Grignard reagent prepared from ethyl bromide and magnesium followed by quenching with para-formaldehyde in dry THF afforded compound 12 in 85% yield (Scheme 2). The treatment of 12 with lithium aluminum hydride (LAH) in dry THF at room temperature furnished the allylic alcohol 13 in 80% yield. The allylic alcohol 13 upon hydride (LAH) in dry THF at room temperature furnished compound 11 in 81% yield [9]. The compound 11 was treated with the Grignard reagent prepared from ethyl bromide and magnesium followed by quenching with para-formaldehyde in dry THF afforded compound 12 in 85% yield (Scheme 2). The treatment of 12 with lithium aluminum hydride (LAH) in dry THF at room temperature furnished the allylic alcohol 13 in 80% yield. The allylic alcohol 13 upon hydride (LAH) in dry THF at room temperature furnished compound 11 in 81% yield [9]. The compound 11 was treated with the Grignard reagent prepared from ethyl bromide and magnesium followed by quenching with para-formaldehyde in dry THF afforded compound 12 in 85% yield (Scheme 2). The treatment of 12 with lithium aluminum hydride (LAH) in dry THF at room temperature furnished the allylic alcohol 13 in 80% yield. The allylic alcohol 13 upon hydride (LAH) in dry THF at room temperature furnished compound 11 in 81% yield [9].}

**Scheme 2. Reagents and conditions.** a) NaH, PMBBr, dry THF, 0°C, 6h, 81%; b) Mg, EtBr (CH₂)₃Br, dry THF, 0°C, 4h, 85%; c) LAH, dry THF, 0°C, 4h, 80%; d) Ti(O₂Pr)₄ (-) DET, Cumene hydroperoxide, dry CH₂Cl₂, -78°C, 6h, 70%; e) Imidazole, TBP, I₂, CH₂CN:Ether, 0°C, 30min, 81%; f) Zn, EtOH, reflux, 30min, 85%; g) MOMCl, DIPEA, dry CH₂Cl₂, 0°C, rt, 2h, 88%; h) DDQ, CH₃Cl, H₂O (9:1), 2.5h, 75%; i) IBX, DMSO, dry CH₂Cl₂, 0°C, 2h, 72%; j) NaH, dry THF, 0°C, rt, 1.5h, 85%; k) p-TSA, dry benzene, 12h, 85%.

**Scheme 3. Reagents and conditions.** a) PMB imidate, PTSA, dry CH₂Cl₂, 0°C, 4h, 90%; b) LiBH₄, EtOH, THF, -10°C, 2h, 90%; c) IBX, DMSO, dry CH₂Cl₂, 0°C, 2h, 85%; d) CH₃PPh₃Br, n-BuLi (1.6 M) to afford alkene 23 in 60% yield [16]. The hydroboration of compound 23 using BH₃, Me₂S complex in dry THF afforded alcohol 24 in 65% yield and the free hydroxyl group was silylated with TBDPS-Cl to furnish the protected compound 25 in 92% yield. Subsequently the oxidative removal of the PMB ether with DDQ in CH₂Cl₂/H₂O (9:1) gave alcohol 26 in 85% yield. The primary hydroxyl group of 26 was subjected to oxidation with IBX to yield the compound 27 in 82% yield. The Z-alkene 28 was obtained from aldehyde 18 using Horner-Wadsworth-Emmons Olefination protocol [15]. The compound 19 was treated with catalytic amount of p-TSA in dry benzene results in the formation of C₁-C₆ fragment 2 in 85% yield (Scheme 2).

**Synthetic Strategy for C₁-C₆ Fragment (2)**

The construction of the C₁-C₆ fragment was initiated with the preparation of protected (5)-(-) Roche ester 20 from (5)-(+)-Roche ester 8 using PMB imidate and p-TSA in 90% yield (Scheme 3). The reduction of ester 20 was treated with LiBH₄ generated in situ in dry THF to afford alcohol 21 in 90% yield. This alcohol was oxidized with IBX to give aldehyde 22 in 85% yield and homologated with (methylene) triphenyl phosphorane in dry THF using n-BuLi (1.6 M) to afford alkene 23 in 60% yield [16]. The hydroboration of compound 23 using BH₃, Me₂S complex in dry THF afforded alcohol 24 in 65% yield and the free hydroxyl group was silylated with TBDPS-Cl to furnish the protected compound 25 in 92% yield. Subsequently the oxidative removal of the PMB ether with DDQ in CH₂Cl₂/H₂O (9:1) gave alcohol 26 in 85% yield. The primary hydroxyl group of 26 was subjected to oxidation with IBX to yield the compound 27 in 82% yield. The Z-alkene 28 was obtained from aldehyde 18 using Horner-Wadsworth-Emmons Olefination protocol [15]. The compound 28 was treated with Dibal-H in anhydrous CH₂Cl₂ at -78°C to afford the allyl alcohol 29 in 90% yield. This alcohol was oxidized with IBX to give aldehyde 30 in 80% yield and homologated with (methylene) triphenyl phosphorane in dry THF using n-BuLi (1.6 M) to afford alkene 31 in 65% yield [16]. The compound 31 was desilylation with TBAF led to the construction of the C₁-C₁₂ fragment 5 in 85% yield (Scheme 3).

**Synthetic Strategy for C₇-C₂₂ Fragment (5)**

As depicted in Scheme 4, the construction of the C₁₃-C₂₂ segment was initiated with the preparation of benzyl protected compound 32 from bicyclic alcohol 10 [17]. The bicyclic olefin 32 was subjected to the key desymmetrization reaction using the chiral hydroboration reaction of Brown et al. [18] to afford the required alcohol 33 in 90% yield with good enantio and regioselectivity. The alcohol 33 was oxidized with PCC [19] to furnish the...
corresponding ketone 34 in 85% yield. The ketone 34 was further oxidized to yield lactone 35 in 90% under Bayer-Villiger conditions [20]. The bicyclic lactone 35 was then subjected to enolization using LDA in THF at -78°C followed by treatment with Ethyl iodide to furnish the ethylated lactone 36 as single diastereomer in 85% yield. Reductive ring-opening of the lactone 36 using excess LiAlH4 resulted in the triol 38 in 80% yield with four chiral centers. The 1, 3-diol functionality in triol 38 was protected as the acetonide using 2, 2-DMP and catalytic amount p-TSA in CH2Cl2 at 0°C to afford 37 in 80% yield and the free hydroxyl group was Pivolyalted with Pivoly chloride to furnish the fully protected triol 38 in 85% yield. Subsequently, the deprotection of acetonide group with p-TSA MeOH led to the diol 39 in 75% yield. The secondary primary hydroxyl group of compound 39 was tosylated with tosyl chloride to afford the compound 40 in 70% yield. The reductive cleavage of triol 38 in 85% yield. Subsequently, the deprotection of acetonide group of compound 40 was tosylated with tosyl chloride to afford the compound 41 in 85% yield. Debenzylation of compound 41 was silylated using TBDMSOTF [21] and 2, 6-lutidine to give 42 in 85% yield. The reductive cleavage of pivaloyl group as well as tosyl group in compound 42 with LiAlH4 to yield alcohol 42 in 45% yield. Debenzylation of compound 42 using Li metal and liq NH3 to afford the compound 43 in 85% yield. Primary hydroxyl group of diol compound 43 was selectively oxidized under Swern [22] oxidation conditions using (COCl)2, DMSO and Et,N at -78°C followed by Wittig reaction with carboxyaryltrimethylphosphorane, in refluxing dry CH2Cl2 to give α, β-unsaturated ester 44 in 80% overall yield for the two step sequence (Scheme 4).

Scheme 5. Reagents and conditions. a) IBX, DMSO, dry CH2Cl2, 0°C-rt, 2h, 85%; b) DMSO, n-BuLi, dry toluene, -78°C-rt, 12h, 60%; c) Gurbb's-II, dry CH2Cl2, reflux, 12h.

The α, β-unsaturated ester 44 on DIBAL-H [23] reduction gave allylic alcohol 45 in 85% yield, which was then converted to allyl bromide 46 using PPh3, 2, 6 lutidine and CBr4 in dry CH2CN in 93% yield. The allylic bromide 46 was converted to its phosphonium salt 6 using PBr3, completing the synthesis of C13-C22 fragment.

Synthesis of C6-C22 fragment (3)

The primary hydroxyl group of 5 was subjected to oxidation with IBX to yield the compound 47 in 85% yield and the coupling of 47 was done by treatment with phosphonium salt 6 in the presence of LiCH2S(O)CH3 in toluene at -78°C to give C6-C22 fragment 3 in 60% yield (Scheme 5). All that remained to complete the synthesis of (-)-callystatin A (1) is to couple the fragment 3, with the lactone 2 and followed by functional group manipulations. But, however the cross-metathesis reaction between the diene 3 and vinyl lactone 2 in the presence of Grubbs's-II catalyst failed to give the product, instead the formation of dimer of vinyl lactone 2 was observed as major product. Due to the high reactivity of vinyl lactone with Grubbs's catalyst, it undergoes self condensation rather than a condensation with the other fragment 3.

Conclusion

In conclusion, we have accomplished the C1-C6 and C7-C22 Fragments of (-)-callystatin A in a highly convergent way, by using desymmetrization strategy and Horner-Wadsworth-Emmons reaction.

Experimental Section

General

All reactions were carried out under an inert atmosphere of argon or nitrogen using standard syringe, septa, and cannula techniques unless otherwise mentioned. Commercial reagents were used without further purification. All solvents were purified by standard techniques. Infrared (IR) spectra were recorded with a Perkin–Elmer 683 spectrometer with NaCl optics. Spectra were calibrated against the Polystyrene absorption at 1610 cm–1. Samples were scanned neat, in KBr wafers or in chloroform as a thin film. 1H NMR spectra were recorded in CDCl3 with a Bruker 300, Varian Unity 500 NMR spectrometer. 13C NMR spectra were recorded at 75MHz in CDCl3, using Tetramethylsilane as the reference standard. Column chromatography was performed using silica gel (60-120 mesh) and the column was usually eluted with ethyl acetate-petroleum ether. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light or
by dipping the plates to sulphuric acid-β-naphthol or to ethanolic anisaldehyde-sulphuric acid-acetic acid or to phosphomolybdic acid-sulphuric acid solution and heating the plates at 120°C. Mass spectra were obtained on a Finnigan MAT1020B or micromass VG 70-70H spectrometer operating at 70 eV using a direct inlet system. Optical rotations were recorded on high sensitive polarimeter with 10mm cell.

1-[3-butyloxy]methyl-4-methoxybenzene (11)

To a stirred suspension of freshly activated NaH (17.14 g, 714.28 mmol) in dry THF (150 mL) under N₂ atmosphere was added 7 (20.0 g, 285.70 mmol) in dry THF (50 mL) in a dropwise manner at 0°C. After stirring for 30 min at 0°C, PMB-Br (22.14 g, 285.70 mmol) was added dropwise. The reaction mixture was stirred for 6 h at 0°C, and quenched with saturated KBr solution. The layers were separated and aq. layer was extracted with ethyl acetate (2x100 mL). The combined organic layers were washed with water, brine solution and then dried over anhydrous Na₂SO₄. Solvent was removed in vacuo and the residue was purified by silica gel column chromatography (EtOAc/pet.ether, 1:9) to afford allyl alcohol 13 (33.9 g, 80% yield) as a clear liquid. 1 H NMR (CDCl₃, 400 MHz): δ 4.39 (s, 2H), 4.02-3.98 (m, 2H), 3.78 (s, 3H), 3.44 (t, 2H, J = 6.4 Hz), 2.37-2.24 (m, 2H), 1.98 (brs, OH). IR (Neat):349, 2935, 2855, 1736, 1609, 1512, 1246, 1032, 971 cm⁻¹. ESIMS: m/z 245 [M + Na]⁺.

(2R,3R)-3-[(4-methoxybenzyl)oxy]ethyloxyran-2-yl) methanol (14)

100ml dry DCM was added to 4°A powdered, activated molecular sieves (2 g) and the suspension mixture was cooled to –20°C. D (-) DET (6.12 g, 29.72 mmol) and Ti(OiPr)₄ (9.38 mL, 29.27 mmol) were added subsequently with stirring and the reacting mixture was stirred for 30 min at –20°C. Allyl alcohol 13 (33.0 g, 148.64 mmol) in dry DCM (100 mL) was added and the resulting mixture was stirred for another 30 minutes at –20°C, cumenehydroperoxide (32 mL, 215.78 mmol) was added and the resulting mixture was stirred at the same temperature for 6 h. After completion of the reaction, (monitored by TLC) it was warmed to 0°C, quenched with 10 mL water and stirred for 1 h at 0°C. 30% aqueous NaOH solution saturated with NaCl (10 mL) was then added and the resulting mixture was stirred vigorously for another 30 min at 0°C. The resulting mixture was vacuum filtered through Celite and the filter cake was washed well with DCM. The organic phase was separated and aqueous phase was extracted with DCM (2 x 100 mL), the combined organic phases were washed with brine, dried over anhydrous Na₂SO₄. Removal of solvent under reduced pressure and purified by silica gel (EtOAc/petether, 4:6) chromatography gave the epoxide 14 (24.7 g, 70% yield) as a viscous liquid. [α]D²⁵: +24.1 (ε = 1, CHCl₃). 1 H NMR (CDCl₃, 300 MHz): 8 7.19 (d, 2H, J = 8.5 Hz), 6.82 (d, 2H, J = 8.3 Hz), 4.41 (s, 2H), 3.78 (3H), 3.62-3.47 (m, 4H), 3.07-2.98 (m, 2H), 2.98-2.86 (m, 1H), 1.92-1.72 (m, 2H). 13 C NMR (CDCl₃, 75 MHz):δ 159.1, 130.1, 129.1, 113.7, 72.6, 66.4, 61.6, 56.4, 55.1, 53.6, 31.9. IR (Neat):3424, 2926, 2631, 1613, 1513, 1247, 1175, 1093, 1031, 819 cm⁻¹. EIMS: m/z 239 [M + H]⁺.

(E)-5-[(4-methoxybenzyl)oxy]-2-penten-1-ol (13)

To a stirred suspension of LiAlH₄ (10.88 g, 286.36 mmol) in dry THF (40 mL) at 0°C was added dropwise a solution of 12 (42.0 g, 190.91 mmol) in dry THF (150 mL) under nitrogen. The reaction mixture was allowed to warm to room temperature and then refluxed for 4 h. It was then cooled to 0°C, diluted with ether and quenched by dropwise addition of saturated aqueous Na₂SO₄ (30 mL). The solid material was filtered and washed thoroughly with hot ethyl acetate several times. The combined organic layers were dried over anhydrous Na₂SO₄. Solvent was removed in vacuo and the residue was purified by silica gel column chromatography (EtOAc/petether, 2:8) to afford allyl alcohol 13 (33.9 g, 80% yield) as a clear liquid. 1 H NMR (CDCl₃, 400 MHz): 8 7.12 (d, 2H, 8.9 Hz), 6.82 (d, 2H, J = 8.9 Hz), 5.67-5.61 (m, 2H), 4.39 (s, 2H), 4.02-3.98 (m, 2H), 3.78 (s, 3H), 3.44 (t, 2H, J = 6.4 Hz), 2.37-2.24 (m, 2H), 1.98 (brs, OH). IR (Neat):3449, 2935, 2855, 1736, 1609, 1512, 1246, 1032, 971 cm⁻¹. ESIMS: m/z 245 [M + Na]⁺.

(2R,3R)-3-[(4-methoxybenzyl)oxy]-1-penten-3-ol (4)

To a stirred suspension of 15 (28.0 g, 80.45 mmol) and zinc (52.2 g, 804.50 mmol) in anhydrous EtOH (100 mL) was refluxed for 30 min. The reaction mixture was filtered on Celite pad and concentrated under reduced pressure, crude product was purified by column chromatography (EtOAc/petether, 3:7) to furnish 4(15.18 g, 85%) [α]D²⁵: +9.3 (ε = 1, CHCl₃). 1 H NMR (CDCl₃, 400 MHz): δ 7.19 (d, 2H, J = 8.5 Hz), 6.82 (d, 2H, J = 8.3 Hz), 4.41 (s, 2H), 3.78 (3H), 3.62-3.47 (m, 4H), 3.07-2.98 (m, 2H), 2.98-2.86 (m, 1H), 1.88-1.74 (m, 2H). IR (Neat):3424, 2926, 2631, 1613, 1513, 1247, 1175, 1093, 1031, 819 cm⁻¹. EIMS: m/z 239 [M + H]⁺.
To a stirred solution of compound 4 (14.0 g, 63.06 mmol) in anhydrous dichloromethane (50 mL) at 0°C under nitrogen, PrNEt (32.9 mL, 189.18 mmol) was added followed by slowwise addition of MOMCl (9.5 mL, 126.12 mmol). After stirring for 2 h at room temperature, the reaction mixture was diluted with water, saturated aqueous NH4Cl solution and then dried over anhydrous Na2SO4. The residue was concentrated under vacuo and purified by silica gel column chromatography (EtOAc/pet.ether, 1:9) to afford the pure compound 16 (14.17 g, 88%) as a colorless oil.

1H NMR (CDCl3, 400 MHz): δ 7.18 (d, 2H, J = 8.3 Hz), 6.81 (d, 2H, J = 8.3 Hz), 5.69–5.62 (m, 1H), 5.16 (dd, 2H, J = 10.4, 18.7 Hz), 4.63 (d, 1H, J = 6.2 Hz), 4.47 (d, 1H, J = 6.2 Hz), 4.39 (s, 2H), 3.78 (s, 3H), 3.78–3.77 (m, 1H), 3.55–3.51 (m, 1H), 3.48–3.43 (m, 1H), 3.31 (s, 3H), 1.88–1.81 (m, 1H), 1.79–1.72 (m, 1H). IR (Neat): 3443, 2934, 2861, 1612, 1512, 1247, 1092, 819 cm−1. ESIMS: m/z 256 [M + Na]+.

(3R)-3-(methoxymethoxy)-4-pentenylbenzene (16)

To a stirred solution of compound 4 (14.0 g, 63.06 mmol) in dry DCM (20 mL) and water (3 mL) was added DDQ (16.8 g, 74.33 mmol). After stirring for 2.5 h at room temperature before being quenched by the slow addition of aq. NaHCO3, dried over anhydrous Na2SO4. Concentration under vacuum. The crude product was purified by column chromatography on silica gel (EtOAc/pet.ether, 0.5:9.5) to give an α, β-unsaturated ester 19 (4.1 g, 85%) as a viscous liquid.

1H NMR (CDCl3, 400 MHz): δ 6.83 (m, 1H), 6.02 (dd, 1H, J = 2.5, 11.1 Hz), 5.93 (m, 1H), 5.40 (d, 1H, J = 17.1 Hz), 5.28 (d, 1H, J = 11.1 Hz), 4.95–4.85 (m, 1H), 2.49–2.39 (m, 2H); 13C NMR (CDCl3, 75 MHz): δ 163.8, 144.4, 134.7, 121.4, 117.8, 77.7, 79.2; IR (neat): 2942, 2927, 1638, 1384, 1249, 1032, 763 cm−1; EIMS: m/z 283 [M + Na]+.

(6R)-6-vinyl-5, 6-dihydro-2H-2-pyranone (2)

To a stirred solution of compound 19 (4 g, 32.25 mmol) in dry benzene (30 mL) was added catalytic amount of PPTS under nitrogen atmosphere. The reaction mixture was refluxed overnight. The aqueous layer was extracted twice with EtOAc, dried over anhydrous Na2SO4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (EtOAc/pet.ether, 7:3) to give the lactone 2 (1.9 g, 85%) as a colorless liquid.

1H NMR (CDCl3, 400 MHz): δ 5.76 (m, 1H), 5.23 (dd, 1H, J = 6.8 Hz), 4.51 (s, 2H), 3.78 (s, 3H), 3.24–3.19 (m, 1H), 2.76–2.69 (m, 1H), 1.15 (d, 3H, J = 6.8 Hz). 13C NMR (CDCl3, 100 MHz): δ 145.5, 137.4, 121.2, 117.4, 93.8, 76.3, 59.4, 55.4, 34.6, 14.2. IR (neat): 1612, 1512, 1249, 1032, 763 cm−1; EIMS: m/z 237 [M + Na]+.

(2R)-2-[4-(methoxymethyl)oxy]-2-methylpropanoate (20)

In a 100 mL round bottomed flask, fitted with a nitrogen adaptor, the methyl (2S)-3-hydroxy-2-methylpropanoate 8 (5 g, 42.37 mmol) in dry CH2Cl2 (30 mL) was taken and catalytic amount of PPTS was added. Then the reaction mixture was cooled to 0°C. To this PMB imidate (14.28 g, 50.84 mmol) in dry THF (15 mL) was added drop wise. After stirring for 1 h, reaction mixture was diluted with 10 mL of Et2O and quenched by the slow addition of 10 mL of H2O. The layers were separated, and the aqueous phase was extracted with two 10 mL portions of EtO. The organic extract was washed with brine solution, dried over anhydrous Na2SO4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (EtOAc/pet.ether, 0.5:9.5) to afford an α, β-unsaturated ester 19 (4.1 g, 85%) as a viscous liquid.

1H NMR (CDCl3, 400 MHz): δ 6.83 (m, 1H), 6.02 (dd, 1H, J = 2.5, 11.1 Hz), 5.93 (m, 1H), 5.40 (d, 1H, J = 17.1 Hz), 5.28 (d, 1H, J = 11.1 Hz), 4.95–4.85 (m, 1H), 2.49–2.39 (m, 2H); 13C NMR (CDCl3, 75 MHz): δ 163.8, 144.4, 134.7, 121.4, 117.8, 77.7, 79.2; IR (neat): 2942, 2927, 1638, 1384, 1249, 1032, 763 cm−1; EIMS: m/z 147 [M + 23].
In two neck round bottomed flask weigh LiCl (4.65 g, 110.9 mmol) keep under nitrogen atmosphere, weigh NaBH₄ (4.21 g, 110.9 mmol) and grind it to make powder very quickly and add to the above R.B. keeping R in ice, add EtOH to the above mixture while stirring. Dissolve the compound 20 in freshly prepared dry THF and add slowly and gradually to the above reaction. Mixture being maintained at -10°C (ice+salt) check the TLC after 2 h. After completion of the reaction distill out EtOH and quench with saturated solution of NH₄Cl and the organic layer was washed with water, aq. NaHCO₃, dried over anhydrous Na₂SO₄. Concentration under reduced pressure and purification over silica gel column chromatography (EtOAc/hexane, 2:8) afforded pure 21 (6.9 g, 90%) as a viscous liquid; [α] D²⁵: (+) 3.1 ([c = 1, CHCl₃]; 1H NMR (CDCl₃, 300 MHz): δ 6.98 (d, 1H, J = 1.5 Hz), 7.18 (d, 2H, J = 9.1 Hz), 6.82 (d, 2H, J = 8.3 Hz), 4.42 (s, 2H), 3.79 (s, 3H), 3.63-3.54 (m, 2H), 2.59 (m, 1H), 1.11 (d, 3H, J = 7.5 Hz); IR (neat): 2960, 2855, 1709, 1611, 1513, 1248, 1091 cm⁻¹; EIMS: 233 (M⁺ + 23).}

To a stirred solution of 23 (3.2 g, 15.53 mmol) in dry THF (15 mL) under N₂ atmosphere was added BH₃. Me₂S (11.6 mL, 23.50 mmol) at 0°C. The mixture was allowed to warm to room temperature and stirred for 3 h. It was then cooled to 0°C and excess borane was quenched by careful addition of water. The reaction mixture was then treated with 20% aqueous NaOH solution (10 mL), 30% H₂O₂ and the resulting mixture was stirred at room temperature for 4 h. Excess H₂O₂ was quenched with saturated aqueous sodium metabisulphite solution and compound was extracted with EtOAc. The organic layer was washed with water, brine and dried over anhydrous Na₂SO₄. Removal of solvent under reduced pressure and purification by silica gel (EtOAc/hexane, 28) column chromatography afforded 24 (2.26 g, 65%) as a viscous liquid; [α] D²⁵: (+) 3.1 ([c = 1, CHCl₃]; 1H NMR (CDCl₃, 200 MHz): δ 7.20 (d, 2H, J = 8.7 Hz), 6.82 (d, 2H, J = 8.7 Hz), 4.42 (s, 2H), 3.79 (s, 3H), 3.67-3.54 (m, 2H), 3.34-3.21 (m, 2H), 2.52 (br, s, 1H), 1.92-1.86 (m, 1H), 1.61-1.51 (m, 2H), 0.93 (d, 3H, J = 7.3 Hz); IR (neat): 3415, 2867, 1612, 1512, 1247, 1035, 819 cm⁻¹; EIMS: 225 (M⁺ + 1).

**tert-butyl(3-R)-4-[(4-methoxybenzyl)oxy]-3-methylbutan-1-ol (25)**

To a mixture of the alcohol 24 (2.1 g, 9.37 mmol) and imidazole (0.701 g, 10.31 mmol) in dry CH₂Cl₂ (10 mL) was added TBDPSCl (2.56 g, 9.37 mmol) at 0°C. The mixture was stirred for 2h. at room temperature. The reaction mixture was diluted with water, washed with saturated aq NaCl and dried over anhydrous Na₂SO₄. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:9) to afford the pure silyl ether 25 (3.98 g, 92%) as a viscous liquid; [α] D²⁵: (+) 17.0 ([c = 1, CHCl₃]; 1H NMR (CDCl₃, 200MHz): δ 7.65-7.59 (m, 4H), 7.39-7.29 (m, 6H), 7.16 (d, 2H, J = 8.3 Hz), 6.79 (d, 2H, J = 8.3 Hz), 4.35 (s, 2H), 3.78 (s, 3H), 3.67 (t, 2H, J = 6.7 Hz), 3.27-3.14 (m, 2H), 1.99-1.89 (m, 1H), 1.75-1.64 (m, 1H), 1.41-1.31 (m, 1H), 1.03 (s, 9H), 0.89 (d, 3H, J = 6.7 Hz); 13 CNMR (CDCl₃, 75MHz): δ 138.5, 134.7, 129.6, 129.4, 129.7, 127.5, 113.6, 75.5, 72.4, 62.5, 55.2, 36.4, 30.2, 26.8, 26.5, 19.1, 17.2; IR (neat): 2936, 2858, 1612, 1466, 1246, 1105, 819 cm⁻¹; EIMS: 480 (M⁺ + NH₄⁺).

**(2-R)-3-[(4-methoxybenzyl)oxy]-2-methylpropan-1-ol (21)**

To a solution of (Methyl) triphenylphosphonium iodide (22.2 g, 54.63 mmol) in dry THF (30 mL), e-BuLi (20.3 mL, 32.62 mmol, 1.6M sol in n-Hexane) was added at 0°C under nitrogen atmosphere and stirred for 30 min. After that period, a clear red colored solution was obtained. At ~78°C, a solution of aldehyde 22 (5.6 g, 27.18 mmol) in dry THF (20 mL) was added drop wise to the reaction mixture was allowed to stir at room temperature for 5 h. A saturated aqueous NH₄Cl solution was added and the resulting mixture was stirred for 2.5 h at room temperature before being quenched by the addition of 10 mL of saturated aqueous NaHCO₃. The layers were separated and aqueous layer was extracted twice with CH₂Cl₂. The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (EtOAc/hexane, 1:9) to give the compound 23 (3.2 g, 15.53 mmol) as a viscous liquid; [α] D²⁵: (+) 17.0 ([c = 1, CHCl₃]; 1H NMR (CDCl₃, 300 MHz): δ 7.19 (d, 2H, J = 8.6 Hz), 6.82 (d, 2H, J = 8.4 Hz), 4.42 (s, 2H), 3.79 (s, 3H), 3.61-3.51 (m, 2H), 3.48 (t, 1H, J = 4.5 Hz) 3.34 (t, 1H, J = 8.8 Hz), 2.42 (br, s, 1H), 2.01 (m, 1H), 0.87 (d, 3H, J = 6.9 Hz); IR (neat): 3151, 2867, 1612, 1512, 1247, 1035, 819 cm⁻¹; EIMS: 231 (M⁺ + 23).
(Z)-4-[1-tert-butyl]-1,1-diphenylsilyl]oxy-2-methylbutanal (27)

To an ice-cooled solution of iodoxybenzoic acid (2.71 g, 9.67 mmol) in DMSO (5 ml) was added a solution of alcohol 26 (2.2 g, 64.3 mmol) in dry CH₂Cl₂ (10 ml). After stirring for 2 h at room temperature, the reaction mixture was filtered through a celite pad and washed with ether. The combined organic layers were washed with water, brine solution and dried over anhydrous Na₂SO₄ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (EtOAc/hexane, 0.5:9.5) to give an aldehyde 27 (1.9 g, 82%) as a viscous liquid.; [α] D²⁵: (+) 28.4 (c = 1, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 8.96 (d, 1H, J = 1.5 Hz), 7.66-7.78 (m, 4H), 7.41-7.51 (m, 6H), 3.75-3.62 (m, 2H), 2.61-2.51 (m, 1H), 1.06-1.93 (m, 1H), 1.08 (d, 3H, J = 7.5 Hz), 1.03 (s, 9H); ¹³C NMR (CDCl₃, 75 MHz): δ 168.2, 144.9, 135.5, 133.9, 132.7, 129.4, 127.5, 62.2, 59.9, 51.4 (m, 1H), 1.05 (s, 9H), 1.02 (t, 3H, J = 3.2 Hz), 0.92 (d, 3H, J = 6.7 Hz); ¹⁴C NMR (CDCl₃, 75 MHz): δ 140.1, 135.6, 135.5, 132.6, 129.7, 129.6, 127.6, 62, 60.6, 39.9, 28.3, 28.1, 26.8, 21.8, 19.1, 12.9; IR(KBr): 3429, 3068, 2930, 2861, 1631, 1464, 1427, 1106, 1101,702 cm⁻¹; EIMS: 397(M⁺ + 1).

Ethyl(Z,4 R)-6-[1-tert-butyl]-1,1-diphenylsilyl]oxy-2-ethyl-4-methyl-2-hexenoate (28)

A solution of the phosphonium salt S-II (1.94 g, 5.17 mmol) in dry THF (5 ml) was added over a cooled (0°C) suspension of NaH (0.225 g, 9.41 mmol) in THF (5 ml). After the mixture was stirred for 30 min at 0°C, the reaction mixture was cooled to -78 °C before being quenched with EtOAc (5 mL). The mixture was allowed to warm to ambient temperature before an aqueous solution of (-) 25 (1.31 g, 90%) as a pale yellow oil.; [α] D

(3R,4Z)-5-ethyl-3-methyl-4,6-heptadienyl oxydiphenylsilane(31)

To a solution of (Methyl) triphenylphosphonium iodide (1.66 g, 4.06 mmol) in dry THF (10 ml), n-BuLi (1.5 mL, 1.26 mmol, 1.6M sol in n-Hexane) was added at 0°C under nitrogen atmosphere and stirred for 30 min. After that period, a clear red colored solution was obtained. At ~78°C, a solution of aldehyde 30 (0.8 g, 2.03 mmol) in dry THF (5 ml) was added drop wise to the reaction mixture was allowed to stir at room temperature for 5h. A saturated aqueous NaH₂PO₄ solution was added and extracted with EtOAc. The organic layer was washed with water, brine and dried over anhydrous Na₂SO₄. Solvent was removed under reduced pressure and purification by column chromatography (EtOAc/hexane, 0.3:9.7) column chromatography afforded 31 (0.516 g, 65%) as a viscous liquid.; [α] D²⁵: (+) 4.4 (c = 1, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 7.64-7.59 (m, 4H), 7.38-7.29 (m, 6H), 6.79 (d, 1H, J = 11.3, 17.4 Hz), 5.19 (d, 1H, J = 17.4 Hz), 5.02 (dd, 2H, J = 9.2, 21.5 Hz), 3.59 (t, 2H, J = 7.1 Hz), 2.92-2.84 (m, 2H, J = 7.1, 14.3 Hz), 1.63-1.36 (m, 1H), 1.46-1.36 (m, 1H), 1.03 (s, 9H), 1.02 (t, 3H, J = 7.1 Hz), 0.95 (d, 3H, J = 6.1 Hz); ¹³C NMR (CDCl₃, 75 MHz): δ 137, 135.5, 134, 133.2, 132.7, 129.4, 127.5, 62.2, 59.9, 40, 30.2, 27.2, 26.7, 20.8, 20.4, 19.2, 14.2, 13.6; IR (neat): 2961, 2932, 1713, 1644, 1107, 703 cm⁻¹; EIMS: 439 (M⁺ + 1).

(3R,4Z)-5-ethyl-3-methyl-4,6-heptadien-1-ol (30)

To a solution of the compound 3 (0.4 g, 1.02 mmol) in THF (5 ml) was added 1M solution of n-BuLi (1.22 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After completion of the reaction diluted with ether. The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulted crude product was purified on silica gel column chromatography (EtOAc/hexane, 1:9) to afford a colorless liquid 5 (0.133 g, 85%).; [α] D²⁵: (+) 25.6 (c = 1, CHCl₃); ¹H NMR (CDCl₃, 500 MHz): δ 3.98 (dd, 1H, J = 4.9, 12.8 Hz), 3.71-3.55 (m, 2H), 2.896-2.73 (m, 1H), 2.12 (q, 2H, J = 7.3, 14.9 Hz), 1.88-1.74 (m, 1H), 1.53-1.45 (m, 1H), 1.05 (s, 9H), 1.02 (t, 3H, J = 3.2 Hz), 0.92 (d, 3H, J = 6.7 Hz); ¹³C NMR (CDCl₃, 75 MHz): δ 8.140, 135.6, 135.5, 132.6, 129.7, 129.6, 127.6, 62, 60.6, 39.9, 28.3, 28.1, 26.8, 21.8, 19.1, 12.9; IR(KBr): 3429, 3068, 2930, 2861, 1631, 1464, 1427, 1106, 1101,702 cm⁻¹; EIMS: 397(M⁺ + 1).

A 250 ml flask equipped with a septum inlet, a magnetic stirring bar, was charged with 5.05 mL of BH$_3$·SMe$_2$ (50 mmol) and 18 mL of THF. It was cooled to 0°C and 18.3 mL (115 mmol) of (-)-Ipc was added in small fractions to the reaction mixture at 0°C. After stirring the reaction mixture for 3 h, isopropanol (10 mL) was added and the mixture was stirred at ambient temperature for 10 h. TLC monitored the completion of the reaction. The reaction mixture was diluted with dichloromethane and the CH$_2$Cl$_2$ layer was washed with a solution of sodium metabisulphite followed by 5% NaHCO$_3$ solution and water. The organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated to dryness under reduced pressure. The residue was purified by silica gel chromatography to afford the pure lactone 35 (10.68 g, 90%) as a oil. [α]$_D^{25}$: -46.2 (c = 6.5, CHCl$_3$); $^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 7.70-7.15 (m, 5H), 5.46 (s, 1H), 4.60 (ABq, 2H, $J$ = 10.6 Hz), 4.11 (m, 1H), 3.61 (t, 1H, $J$ = 5.2 Hz), 2.75-2.65 (m, 2H), 2.25-2.15 (m, 1H), 2.09-1.98 (m, 1H), 1.18 (d, 3H, $J$ = 7.6 Hz), 0.98 (d, $3H, J$ = 7.6 Hz); IR (Neat): 1755 cm$^{-1}$; FAB mass: m/z 276 (M$^+$).

$\textbf{2 R,3 R,4 S,5 R,6 R} - 5$-( benzylx o)-2-ethyl-4,6-dimethylheptane-1,3,7-triol (9)

To a stirred suspension of LiAlH$_4$ (1.31 g, 34.5 mmol) in dry THF (30 mL) at 0°C, a solution of lactone 36 (6.9 g, 23.0 mmol) in dry THF (30 mL) was added drop wise. The reaction mixture was refluxed for 4 h. It then was cooled to 0°C, diluted with ether and quenched with drop wise addition of saturated aqueous Na$_2$SO$_4$. The solid material was filtered and washed thoroughly with hot ethyl acetate for several times. The combined organic layers were dried over anhydrous Na$_2$SO$_4$. The solvent was removed under vacuum. The resulting lactol compound was purified by TRLC on silica gel chromatography to afford the compound 9 (2.0 g, 49%) as a viscous liquid; [α]$_D^{25}$: +49.0 (c = 1, CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.33–7.23 (m, 5H), 5.34 (d, 1H, $J$ = 3.0 Hz), 4.64 (d, 1H, $J$ = 12.0 Hz), 4.48 (d, 1H, $J$ = 12.0 Hz), 3.76 (d, 1H, $J$ = 4.5 Hz), 3.55 (t, 1H, $J$ = 3.0 Hz), 2.51 (t, 1H, $J$ = 7.5 Hz), 2.19–2.14 (m, 1H), 1.99–2.03 (m, 1H), 1.81 (quintet, 2H, $J$ = 7.5 Hz), 1.13 (d, 3H, $J$ = 7.5 Hz), 0.99 (t, 3H, $J$ = 7.5 Hz), 0.91 (d, 3H, $J$ = 7.5 Hz); $^1$C NMR (CDCl$_3$, 75 MHz): $\delta$ 169.7, 137.7, 129.8, 128.0, 127.3, 99.7, 79.1, 76.5, 73.8, 42.1, 39.6, 37.4, 26.8, 13.3, 13.0, 11.5; IR (Neat): 2969, 1730, 1212, 771 cm$^{-1}$; FAB Mass: m/z 305 (M$^+$+1).

1H NMR (CDCl3, 300 MHz): δ 178.6, 139.1, 128.2, 127.1, 126.6, 97.7, 82.7, 74.8, 71.6, 41.7, 37.7, 32.8, 32.5, 28.2, 27.2, 27.0, 26.1, 25.2, 24.0, 21.9, 19.7, 16.2, 10.7, 9.8; IR (neat): 2960, 1720, 1100 cm⁻¹; FAB mass: m/z 435 (M⁺+1).

2,4,6-trimethyloctane-1,3-diol (43) was added to an ice-cold solution of compound 40 (2.5 g, 8.5 mmol) in dry CH2Cl2 (15 mL). To a stirred suspension of LiAlH4 (0.3 g, 6.04 mmol) in dry THF (10 mL), at 0°C, a solution of compound 41 (2.0 g, 3.02 mmol) was added drop wise. The reaction mixture was stirred for 4 h. It was then cooled to 0°C and treated with ether and quenched with drop wise addition of saturated aqueous Na2SO4. The solid material was filtered and washed thoroughly with hot ethyl acetate for several times. The combined organic layers were dried over anhydrous Na2SO4. The solvent was removed under vacuo and the residue was purified by column chromatography to afford the compound 42 (0.98 g, 80%) as a viscous liquid.; [α]D²⁰ : (-) 20.0 (c = 1, CHCl₃); 1H NMR (CDCl₃, 200MHz): δ 7.72 (d, 2H, J = 8.1 Hz), 7.33-7.29 (m, 7H), 4.57 (s, 2H), 4.27-4.07 (m, 2H), 3.98-3.89 (m, 3H), 3.33-3.27 (m, 1H), 2.44 (s,3H), 2.16-1.68 (m, 3H),1.34-1.41 (m, 2H), 1.20 (s, 9H), 1.10 (s, 3H), 0.88 (s, 3H), 0.80 (s, 3H), 0.76 (s, 3H), 0.01 (s, 3H); IR ( neat): 2970, 1723, 1300, 1170 cm⁻¹; FAB Mass: m/z 663 (M⁺+1).

2 R,3 R,4 S,5 R,6 R-3-(benzylxoy)-5-[1-(tert-buty1)-1,1-dimethylsilyl]oxy-2,4-diethyl-6-(4-methylphenyl)sulfonyloxy)octyl pivalate (41)

tert-butyl dimethylsilyl trifluoromethanesulfonate (1.28 g, 5.47 mmol) was added to an ice-cold solution of compound 40 (2.5 g, 6.56 mmol) in dry CH3Cl (15 mL) followed by the slow addition of 2,6-lutidine (1.59 g, 15.68 mmol). The reaction mixture was stirred for 1 h at 0°C before being diluted with EtOAc and washed with saturated aqueous NH4Cl and brine solution. The organic phase was filtered and washed thoroughly with hot ethyl acetate for several times. The combined organic layers were dried over Na2SO4. The solid material was filtered and washed thoroughly with hot ethyl acetate for several times. The combined organic layers were dried over anhydrous Na2SO4. The solvent was removed under vacuo and the residue was purified by column chromatography to afford the compound 41 (2.56 g, 85%); [α]D²⁰ : (+) 5.4 (c = 0.6, CHCl₃); 1H NMR (CDCl₃, 200MHz): δ 7.72 (d, 2H, J = 8.1 Hz), 7.33-7.29 (m, 7H), 4.57 (s, 2H), 4.27-4.07 (m, 2H), 3.98-3.89 (m, 3H), 3.33-3.27 (m, 1H), 2.44 (s,3H), 2.16-1.68 (m, 3H),1.34-1.41 (m, 2H), 1.20 (s, 9H), 1.10 (s, 3H), 0.88 (s, 3H), 0.80 (s, 3H), 0.76 (s, 3H), 0.01 (s, 3H); IR ( neat): 2970, 1723, 1300, 1170 cm⁻¹; FAB Mass: m/z 663 (M⁺+1).

2 R,3 R,4 S,5 S,6 R-3-(benzylxoy)-5-[1-(tert-buty1)-1,1-dimethylsilyl]oxy-2,4,6-trimethylolctan-1-ol (42)

to a stirred suspension of LiAlH₄, 0.3 g, 6.04 mmol) in dry THF (10 mL) at 0°C was added drop wise a solution of compound 41 (2.0 g, 3.02 mmol) in dry THF (15 mL). The reaction mixture was refluxed for 4 h. It was then cooled to 0°C, diluted with ether and quenched with drop wise addition of saturated aqueous Na2SO4. The solid material was filtered and washed thoroughly with hot ethyl acetate for several times. The combined organic layers were dried over anhydrous Na2SO4. The solvent was removed under vacuo and the residue was purified by column chromatography to afford the compound 42 (0.98 g, 80%) as a viscous liquid.; [α]D²⁰ : (+) 2.5 (c = 1, CHCl₃); 1H NMR (CDCl₃, 200MHz): δ 7.31–7.24 (m, 5H), 4.61 (brs, 2H), 3.75 (t, 2H, J = 2.9 Hz), 3.56–3.45 (m, 2H), 3.34–3.28 (dd, 1H, J = 3.7, 7.4 Hz), 2.60–2.51 (m, 1H), 2.01–1.85 (m, 2H), 1.56–1.40 (m, 2H), 1.14 (d, 3H, J = 6.6 Hz), 0.90 (s, 9H), 0.87 (s, 3H, J = 6.6 Hz), 0.85 (t, 3H, J = 7.4 Hz), 0.82 (d, 3H, J = 6.6 Hz), 0.05 (s, 3H), 0.03 (s, 3H); IR ( neat): 3498, 3072, 2959, 1092, 1050 cm⁻¹; FAB Mass: m/z 409 (M⁺+1).

2 R,3 R,4 S,5 R,6 S-3-(benzylxoy)-5-[1-(tert-buty1)-1,1-dimethylsilyl]oxy-2,4,6-trimethyloloctan-1,3-diol (43)

to a stirred suspension of LiAlH₄, 0.3 g, 6.04 mmol) in dry THF (10 mL) at 0°C was added drop wise a solution of compound 41 (2.0 g, 3.02 mmol) in dry THF (15 mL). The reaction mixture was refluxed for 4 h. It was then cooled to 0°C, diluted with ether and quenched with drop wise addition of saturated aqueous Na2SO4. The solid material was filtered and washed thoroughly with hot ethyl acetate for several times. The combined organic layers were dried over anhydrous Na2SO4. The solvent was removed under vacuo and the residue was purified by column chromatography to afford the compound 42 (0.98 g, 80%) as a viscous liquid.; [α]D²⁰ : (+) 2.5 (c = 1, CHCl₃); 1H NMR (CDCl₃, 200MHz): δ 7.31–7.24 (m, 5H), 4.61 (brs, 2H), 3.75 (t, 2H, J = 2.9 Hz), 3.56–3.45 (m, 2H), 3.34–3.28 (dd, 1H, J = 3.7, 7.4 Hz), 2.60–2.51 (m, 1H), 2.01–1.85 (m, 2H), 1.56–1.40 (m, 2H), 1.14 (d, 3H, J = 6.6 Hz), 0.90 (s, 9H), 0.87 (s, 3H, J = 6.6 Hz), 0.85 (t, 3H, J = 7.4 Hz), 0.82 (d, 3H, J = 6.6 Hz), 0.05 (s, 3H), 0.03 (s, 3H); IR ( neat): 3498, 3072, 2959, 1092, 1050 cm⁻¹; FAB Mass: m/z 409 (M⁺+1).
over a period of 10 min. The reaction mixture was then stirred for another 30 min at –33°C and quenched by the addition of solid ammonium chloride and the ammonia was then allowed to evaporate. The residue left was partitioned between water and the aqueous phase extracted with ether. The organic layers were combined, washed once with water, brine, dried over anhydrous Na2SO4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford the pure 43 (0.56 g, 80%) as a clear colorless liquid.; [α]D20 = -16.3 (ε = 1.5, CHCl3); 1H NMR (CDCl3, 200 MHz): δ 5.55 (d, 1H, J = 9.5), 4.01 (s, 2H), 3.70 (t, 1H, J = 2.9 Hz), 3.61 (d, 1H, J = 10.2, 2.2 Hz), 2.42–2.6 (m, 1H), 1.78–1.70 (m, 1H), 1.68 (d, 3H, J = 1.1 Hz), 1.6 (m, 1H), 1.40–1.20 (m, 2H), 1.05 (d, 3H, J = 6.9 Hz), 0.99 (d, 3H, J = 6.9 Hz), 0.91 (s, 3H), 0.90 (t, 3H, J = 7.3 Hz), 0.73 (d, 3H, J = 6.9 Hz), 0.10 (s, 3H), 0.06 (s, 3H); 13C NMR (CDCl3, 75 MHz): δ 134.4, 126.5, 79.7, 76.1, 68.8, 40.8, 35.5, 34.5, 28.4, 25.4, 17.6, 14.9, 13.4, 11.6, -4.6, -5.1 (IR (neat): 3423, 2930, 2360, 1219, 1013 cm−1); FAB mass: m/z 359 (M+1).

**Ethyl (E,4R,5R,6R,7R,8S)-7-[1-(tert-butyl)-1,1-dimethylsilyl]oxo-5-hydroxy-2,4,6,8-tetramethyl-2-decen-4olate (44)**

In an oven-dried flask under N2 atmosphere DMSO (0.28 mL, 3.93 mmol) was dissolved in dry CH2Cl2 (5 mL). The solution was cooled to –78°C, and (COCl)2 (3.08 mmol) was dissolved in dry CH2Cl2 (5 mL). The solution was allowed to warm to ambient temperature before an aqueous solution of Rochelle’s salt was added (30 mL) and stirred for one hour. The aqueous phase was extracted with CH2Cl2, and the combined organic extracts were dried over anhydrous Na2SO4, concentrated, and purified by column chromatography on silica gel to afford the title desired allylic alcohol 45 (0.55 mmol) as a pale yellow oil.; [α]D20 (c 0.29, CH2Cl2) = -1.1, CHCl3; 1H NMR (CDCl3, 300 MHz): δ 6.98 (dq, 1H, J = 17.6 Hz), 5.25 (d, 1H, J = 7.3 Hz), 5.13 (d, 1H, J = 12.4 Hz), 3.24–3.18 (m, 1H), 2.36 (d, 2H, J = 8.3 Hz), 2.19 (q, 2H, J = 7.2, 15.6 Hz), 1.05 (t, 3H, J = 7.2 Hz), 1.04 (d, 3H, J = 7.2 Hz); 13C NMR (CDCl3, 75 MHz): δ 208.1, 151.3, 134.7, 129.6, 127.6, 51.0, 26.9, 21.2, 18.9, 13.2; IR (neat): 2924, 2853, 1733, 1638, 1460 cm−1; EIMS: m/z 401 (M+1).

**Preparation of phosphonium salt (6)**

Allylic bromide 46 (0.1g, 0.23 mmol) was dissolved in dry acetonitrile (5 mL) and tributylphosphine (0.071g, 0.35 mmol) was added at once. After stirring for 30 min (or until starting material disappeared by TLC) at rt the solvent was evaporated under reduced pressure, and the resulting viscous oil used directly in the next reaction.

(3R,4R,Z)-5-ethyl-3-methyl-4,6-heptadienial (47)

To an ice-cooled solution of iodoxybenzoic acid (0.33 g, 1.18 mmol) in DMSO (3 mL) was added a solution of alcohol 5(0.12 g, 0.78 mmol) in dry CH2Cl2 (3 mL). After stirring for 2 h at room temperature, the reaction mixture was filtered through a celite pad and washed with ether. The combined organic layers were washed with water, brine solution and dried over anhydrous Na2SO4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (EtOAc/hexane, 0.5:9.5) to give an allylic alcohol 47 (0.083 g, 85%) as a viscous liquid; [α]D20 = 47.0 (ε = 1.5, CHCl3); 1H NMR (CDCl3, 300 MHz): δ 6.96 (t, 1H, J = 2.0 Hz), 6.64 (dd, 1H, J = 10.4, 17.6 Hz), 5.25 (d, 1H, J = 17.6 Hz), 5.13 (t, 2H, J = 12.4 Hz), 3.24–3.18 (m, 1H), 2.36 (d, 2H, J = 8.3 Hz), 2.19 (q, 2H, J = 7.2, 15.6 Hz), 1.05 (t, 3H, J = 7.2 Hz), 1.04 (d, 3H, J = 7.2 Hz); 13C NMR (CDCl3, 75 MHz): δ 108.3, 151.3, 134.7, 129.6, 127.6, 51.0, 26.9, 21.2, 18.9, 13.2; IR (neat): 2924, 2853, 1733, 1638, 1460 cm−1; EIMS: m/z 475 (M+ + 23).
A solution of BuLi (1.6 M, 0.131 mL, 0.209 mmol) was added to a solution of DMSO (0.064), in dry toluene (0.55 mL) at room temperature, then the whole was stirred for 45 min. A solution of phophonium salt 6 (0.090 g, 0.154 mmol) and aldehyde 47 (0.020 g, 0.080 mmol) was dissolved in dry toluene (1.2 mL) was added to the solution of dimyl carbonate at -78 °C to 0 °C overnight. The reaction mixture was poured into saturated aqueous NH₄Cl, then dried over MgSO₄. Removal of solvent from the Et₂O extract under reduced pressure gave a product, which was purified by column chromatography Et₂O/pentane 1:9 to furnish a colourless oil (3.067 g, 60% yield); [α]D²⁰: (-) 20.3 (c = 0.5, CHCl₃); 1H NMR (CDCl₃; 200 MHz): δ 6.69-6.56 (m, 1H), 5.91 (dd, 1H, J = 11.5 Hz), 5.53-5.41 (m, 1H), 5.26-5.47 (m, 4H), 3.74-3.53 (m, 2H), 2.71-2.58 (m, 1H), 2.56-2.42 (m, 1H), 2.38-2.24 (m, 1H), 2.19 (q, 2H, J = 7.1, 14.5 Hz), 2.11-2.02 (m, 1H), 1.76 (s, 3H), 1.61-1.52 (m, 1H), 1.48-1.32 (m, 1H), 1.31-1.15 (m, 2H), 1.05 (t, 3H, J = 7.3 Hz), 0.98 (d, 3H, J = 6.7 Hz), 0.97 (d, 3H, J = 6.2 Hz), 0.88 (t, 3H, J = 7.2 Hz), 0.94-0.89 (m, 12H), 0.73 (d, 3H, J = 6.9 Hz), 0.08 (s, 3H), 0.06 (s, 3H); 13C NMR (CDCl₃, 75 MHz): δ 141.2, 133.7, 128.6, 128.5, 127.5, 126.4, 126.0, 110.2, 80.5, 77.6, 41.4, 41.3, 35.8, 35.6, 35.4, 29.7, 29.0, 28.9, 26.2, 26.1, 25.9, 18.1, 17.9, 15.4, 13.8, 12.6, 12.1, 11.8, -4.1, -4.7; IR (neat): 3385, 2960, 2930, 1739, 1596, 1461, 1382, 1253, 1052, 1007, 836, 774 cm⁻¹; EIMS: m/z 499 (M+23).

**Dimer Compound**

To a solution of compound 2 (0.1 g, 0.806 mmol) in PhH (1 mL) was added the compound 3 (0.248 g, 1.61 mmol). The mixture was heated to 55°C, and a solution of second generation Grubbs’ catalyst (0.068 g, 0.080 mmol) in PhH (1 mL) was added via syringe pump. Heating was continued for 12 h after addition was complete. After cooling to room temperature, the mixture was filtered through a short pad of silica gel, and the filtrate was concentrated in vacuo. Purification by flash chromatography (eluent: PE–EtOAc, 2:8) gave metathesis product dimer only. NMR (CDCl₃, 500 MHz): δ 141.9, 133.7, 128.6, 128.5, 127.5, 126.4, 126.0, 110.2, 80.5, 77.6, 41.4, 41.3, 35.8, 35.6, 35.4, 29.7, 29.0, 28.9, 26.2, 26.1, 25.9, 18.1, 17.9, 15.4, 13.8, 12.6, 12.1, 11.8, -4.1, -4.7; IR (neat): 3385, 2960, 2930, 1739, 1596, 1461, 1382, 1253, 1052, 1007, 836, 774 cm⁻¹; EIMS: m/z 499 (M+23).

**Acknowledgement**

KYG thanks UGC, New Delhi for the award of fellowship. Author acknowledges the partial support by King Saud University for Global Research Network for Organic Synthesis (GRNOS).

**References**