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

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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.

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.

Interesting structural features combined with the important biological activity of (-)-callystatin A has attracted several research groups to attempt its total synthesis [3] as well as the synthesis of its analogues.

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.

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

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Synthetic Strategy for C₁⁻C₆ Fragment (2)

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 benzyl ether 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 trans allylic alcohol 13 in 80% yield. The allylic alcohol 13 upon Sharpless Asymmetric epoxidation [10] using (-) DET afforded the corresponding epoxide 14 in 70% yield. The hydroxyl group of 14 was converted into its iso-propyl compound 15 in 81% yield. The compound 14 was converted into a secondary allylic alcohol 4 in 85% yield [11] by refluxing with activated Zinc in dry ethanol. The secondary hydroxyl group 4 was converted into its corresponding methoxy ether using PMBBr and NaH in dry THF in 85% yield [12]. The oxidative removal of the PMB ether with DDQ in CH₂Cl₂/H₂O (9:1) gave alcohol 17 in 75% yield. The primary hydroxyl group of 17 was subjected to oxidation with IBX [14] to yield the compound 18 in 72% yield. The Z-alkene 19 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 C₇-C₁₂ fragment 2 in 85% yield (Scheme 2).

Scheme 2. Reagents and conditions. a) i. NaH, PMBBr, dry THF, 0°C-rt, 6h, 81%; b) Mg, EtOH, (CH₂)₃, dry THF, 0°C-rt, 4h, 85%; c) LAH, dry THF, 0°C-rt, 4h, 80%; d) Ti(O₂)₄ (-) DET, Cumene hydroperoxide, dry CH₂Cl₂, -78°C to 0°C, 6h, 70%; e) Imidazole, TTP, I₃, CH₂CN:Ether, 0°C-rt, 30min, 81%; f) Zn, EtOH, reflux, 30min, 85%; g) MOMCl, DIPEA, dry CH₂Cl₂, 0°C-rt, 2h, 88%; h) DDQ, CH₂Cl₂/H₂O (9:1), 2.5h, 75% ; i) IBX, DMSO, dry CH₂Cl₂, 0°C-rt, 2h, 72%; j) S-II, NaH, dry THF, 0°C-rt, 1.5h, 85%; k) p-TSA, dry benzene, 12h, 85%.

Synthetic Strategy for C₇⁻C₁₂ Fragment (5)

The construction of the C₇⁻C₁₂ 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 afforded 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 allene 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 TBDDS-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 [14] to yield the compound 27 in 82% yield. The Z-alkene 28 was obtained from allene 27 using Horner-Wadsworth-Emmons Olefination protocol [15]. The ester 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 allene 31 in 65% yield [16]. The compound 31 was desilylation with TBAF led to the construction of the C₇⁻C₁₂ fragment 5 in 85% yield (Scheme 3).

Scheme 3. Reagents and conditions. a) i. PMB imidate, PTSA, dry CH₂Cl₂, 0°C-rt, 4h, 90%; b) LiBH₄, EtOH, THF, -10°C, 2h, 90%; c) IBX, DMSO, dry CH₂Cl₂, 0°C-rt, 2h, 85%; d) CH₂PPh₂Br, n-BuLi, dry THF, 0°C-78°C, 5h, 60%; e) BH₃, Me₂S, NaOH, H₂O₂, dry THF, 0°C, 4h, 65%; f) Imidazole, TBDDS-Cl, CH₂Cl₂, 0°C-rt, 2h, 92%; g) DDQ, CH₂Cl₂/H₂O (9:1), 0-rt, 2.5h, 85%; h) IBX, DMSO, dry CH₂Cl₂, 0°C-rt, 2h, 82%; i) NaH, S-II, dry THF, 0°C-78°C, 1.5h, 88%; j) DIBAL-H, -78°C, 2h, 90%; k) IBX, DMSO, dry CH₂Cl₂, 0°C-rt, 2h, 80%; l) CH₂PPh₂Br, n-BuLi, dry THF, 0°C-78°C, 5h, 65%; m) TBAF, THF, 0°C-rt, 1h, 85%.

Synthetic Strategy for C₁₃⁻C₂₂ Fragment (6)

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 37 in 80% yield with four chiral centers. The 1, 3-diol functionality of triol 9 was protected as the acetone using 2, 2-DMP and catalytic amount 4-TSA in CH₂Cl₂ at 0°C to afford 38 in 80% yield and the free hydroxyl group was Pivolyalted with Pivyl chloride to furnish the fully protected triol 38 in 85% yield. Subsequently, the deprotection of acetone group with p-TSA MeOH led to the diol 40 in 75% yield. The primary hydroxyl group of compound 40 was tosylated with tosyl chloride to afford the compound 41 in 70% yield. The secondary hydroxyl group of 41 was silylated using TBDMSOTf [21] and -TSA in CH₂Cl₂ at -78°C to give 42 in 85% yield. The reductive cleavage of pivaloyl group as well as tosyl group in compound 42 with LiAlH₄ to allyl alcohol 42 in 85% yield. Debenzylation of compound 42 using Li metal and liq NH₃ to afford the compound 43 in 80% yield. Primary hydroxyl group of diol compound 43 was selectively oxidized under Swern [22] oxidation conditions using (COCl)₂, DMSO and Et₃N in toluene at -78°C followed by Wittig reaction with carboxyethylidene triphenylphosphorane, in refluxing dry CH₂Cl₂ to give α, β-unsaturated ester 44 in 80% overall yield for the two step sequence (Scheme 4).

Scheme 4. Reagents and conditions. a) (-)Ipc₂BH, NaOH, H₂O₂, 7d, 90%; b) PCC dry CH₂Cl₂, 0°C-rt, 3h, 85%; c) m-CPBA, NaHCO₃, 0°C-rt, 10 h, 90%; d) LDA Ethyl iodide, dry THF, -78°C, 5h, 85%; e) LDA, dry THF, 0°C-rt, 4 h, 80%; f) 2, 2-DMP, p-TSA, 0°C-rt, dry CH₂Cl₂, 12 h, 80%; g) Pivyl chloride, pyridine, dry CH₂Cl₂, 0°C-rt, 12 h, 85%; h) 4-TSA, MeOH, 0°C-rt, 10 h, 75%; i) TsCl, Bu₃SnO, Et₃N, dry CH₂Cl₂, 0°C-rt, 10 h, 70%; j) TBSTF, 2,6-lutidine, dry CH₂Cl₂, 0°C-rt, 1 h, 85%; k) LAH, dry THF, 0°C-rt, 4h, 85%; l) Li, Liq NH₃, dry THF, 30 min, 80%; m) (i) dry DMSO, dry CH₂Cl₂, (COC₁₂)₂, Et₃N, -78°C; (ii) PPh₃=CCH₂CO₂Et, dry benzene, rt, 2h, 80%; n) DIBAL₃, dry CH₂Cl₂, -78°C, 2 h, 80%; o) CB₃p, PPh₃, 2, 6 lutidine, CH₂CN, 30 min., 93%; p) PBu₃, CH₂CN, 30 min.

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

The α, β-unsaturated ester 44 on DIBAL-H [23] reduction gave allylic alcohol 45 in 80% 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 PBu₃, completing the synthesis of C₁₃-C₂₂ fragment.

Synthesis of C₁₃-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 LiCH₂SO(CH₂)₅, in toluene at -78°C to give C₁₃-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 Grubb'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 C₁₋₃₆ and C₁₃₋₂₂ 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 CDC₁₃ with a Bruker 300, Varian Unity 500 NMR spectrometer. ¹³C NMR spectra were recorded at 75MHz in CDC₁₃ 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
1-(3-butyloxy)phenyl-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 (ErOAc/pet.ether, 1:9) to afford 11 (43.9 g, 81% yield) as a viscous liquid. [α]D25: +24.1 (c = 1, CHCl3). 1H NMR (CDCl3, 300 MHz): 8.71 (d, 2H, J = 8.3 Hz), 6.82 (d, 2H, J = 8.3 Hz), 4.45 (s, 2H), 3.78 (s, 3H), 3.52 (t, 2H, J = 7.5 Hz), 2.44 (dt, 2H, J = 2.5, 7.5 Hz), 1.87 (t, 1H, J = 2.5 Hz).

5-[(4-methoxybenzyl)oxy]-2-pentyn-1-ol (12)

Freshly prepared EtMgBr (prepared in situ from 8.14 g (339.16 mmol) of Mg and 26.18 mL (339.16 mmol) of ethyl bromide in 60 mL of dry THF) was added dropwise to stirred solution of alkyne 1 (43.9 g, 226.31 mmol) in dry THF (200 mL) at 0°C. After completion addition, reaction mixture was stirred for 1 h at room temperature and para-formaldehyde (40 g) was added. The resulting mixture was stirred further for 3 h at room temperature and then quenched with saturated aqueous NH4Cl solution. The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with water, brine solution and dried over anhydrous Na2SO4. Concentration under reduced pressure and purification by silica gel column chromatography (ErOAc/pet.ether, 1:9) afforded alcohol 12 in 42.3 g, 85% yield as a viscous liquid. [α]D25: +24.1 (c = 1, CHCl3). 1H NMR (CDCl3, 300 MHz): 8.71 (d, 2H, J = 8.5 Hz), 6.82 (d, 2H, J = 8.5 Hz), 4.41 (s, 2H), 3.78 (s, 3H), 3.63-3.47 (m, 4H), 3.07-2.98 (m, 4H), 2.98-2.86 (m, 1H), 1.92-1.72 (m, 2H). 13C NMR (CDCl3, 75 MHz): 159.1, 130.1, 129.1, 113.7, 72.6, 64.6, 61.5, 56.4, 55.1, 53.6, 31.9. IR (Neat): 3424, 2926, 1631, 1513, 1247, 1175, 1093, 1031, 819 cm⁻¹. EIMS: m/z 239 [M + Na]+.

(2R,3R)-3-[(4-methoxybenzyl)oxy]ethyl oxiran-2-yl) methyl alcohol (14)

To a stirred solution of 14 (24.0 g, 100.84 mmol) in a mixture of methanol (14) (9.38 mL, 29.72 mmol) and TiOiPr (9.38 mL, 29.72 mmol) were added successively with stirring and the resulting mixture was stirred for 30 min at −20°C. Allyl alcohol 13 (53.0 g, 486.64 mmol) in dry DCM (100 mL) was added and the resulting mixture was stirred for another 30 minutes at −20°C. Cumenhydroperoxide (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 (ErOAc/pet.ether, 4:6) chromatography gave the epoxide 14 (24.7 g, 70 % yield), as a viscous liquid. [α]D25: +24.1 (c = 1, CHCl3). 1H NMR (CDCl3, 300 MHz): 8.71 (d, 2H, J = 8.5 Hz), 6.82 (d, 2H, J = 8.5 Hz), 4.41 (s, 2H), 3.78 (s, 3H), 3.63-3.47 (m, 4H), 3.07-2.98 (m, 4H), 2.98-2.86 (m, 1H), 1.92-1.72 (m, 2H). 1C NMR (CDCl3, 75 MHz): 159.1, 130.1, 129.1, 113.7, 72.6, 64.6, 61.5, 56.4, 55.1, 53.6, 31.9. IR (Neat): 3424, 2926, 1631, 1513, 1247, 1175, 1093, 1031, 819 cm⁻¹. EIMS: m/z 239 [M + H]+.

(2S,3R)-2-iodomethyl-3-[(4-methoxybenzyl)oxy]ethyl oxiran-15

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 (ErOAc/pet.ether, 2:8) to afford allyl alcohol 13 (33.9 g, 80% yield) as a clear liquid. 1H NMR (CDCl3, 400 MHz): 8.71 (d, 2H, J = 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, 2835, 2855, 1736, 1609, 1512, 1246, 1032, 971 cm⁻¹. ESIMS: m/z 245 [M + Na]+.

(2R,3R)-3-[(4-methoxybenzyl)oxy]ethyl oxiran-2-yl) methyl alcohol (15)

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 and concentrated under reduced pressure, crude product was purified by column chromatography (ErOAc/pet.ether, 3:7) to furnish 4(15.18 g, 85%) [α]D25: −9.3 (c = 1, CHCl3). 1H NMR (CDCl3, 400 MHz): 8.71 (d, 2H, J = 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, 2835, 2855, 1736, 1609, 1512, 1246, 1032, 971 cm⁻¹. ESIMS: m/z 245 [M + Na]+.
1. Methoxy-[(3R)-(3-methoxymethoxy)-4-pentenyl] benzene (16)

To a stirred solution of compound 4 (14.0 g, 63.06 mmol) in anhydrous dichloromethane (50 mL) at 0°C under nitrogen, Pr₂NEt (32.9 mL, 189.18 mmol) was added followed by drop wise 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, brine 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 (14.75 g, 88%) as a clear viscous liquid. [α]D = +56.1 (c = 0.5, CHCl₃)²

13C NMR (CDCl₃, 75 MHz): δ 136.3, 118.0, 93.7, 72.0, 50.4, 48.7. IR (Neat): 2927, 1721, 1638, 1421, 1217, 1030 cm⁻¹.

methyl (2Z,5R)-5-(methoxymethoxy)-2,6-heptadienoate (19)

A solution of the phosphonate S-I (9.3 g, 26.73 mmol) in dry THF (15 mL) was added to ice cold suspension of NaH (1.16 g, 48.61 mmol) in THF (10 mL). After the mixture was stirred for 30 min at 0°C, the reaction mixture was cooled to −78°C and then a solution of aldehyde 18 (3.5 g, 24.30 mmol) in dry THF (15 mL) was added drop wise. After stirring for 1 h, reaction mixture was diluted with 30 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 Et₂O. 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 give an α, β-unsaturated ester 19 (4.1 g, 41.8%) as a viscous liquid. [α]D = +56.1 (c = 0.5, CHCl₃)²

13C NMR (CDCl₃, 100 MHz): δ 137.4, 134.6, 121.6, 117.8, 77.7, 29.3; IR (neat): 2922, 1720, 1638, 1384, 1249, 1032, 763 cm⁻¹; EIMS: m/z 237 [M + Na]+.

14.44, 134.4, 127.1, 117.8, 93.6, 75.9, 59.8, 55.4, 34.6, 14.2. IR (Neat): 2922, 1720, 1638, 1384, 1249, 1032, 763 cm⁻¹; EIMS: m/z 169 [M + Na]+.

(4R,5R)-1,5-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 washed 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, 5:5) to give the lactone 2 (1.9 g, 85%) as a liquid. [α]D = +82.4 (c = 0.5, CHCl₃)²; 1H NMR (CDCl₃, 300 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 = 1.71 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, 29.2; IR (Neat): 2922, 1720, 1638, 1384, 1249, 1032, 763 cm⁻¹; EIMS: 147 (M⁺ + 23).

(2S)-3-[(4-methoxybenzyl)oxy]-2-methylpropanoic acid (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. After completion of addition, the reaction mixture was heated at 0°C. To this PMB imidate (14.28 g, 50.84 mmol) in dry CH₂Cl₂ (30 mL) was added in one portion. The reaction mixture was stirred 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/pet.ether, 1:9) to give a liquid. [α]D = 0.5, CHCl₃)² to give the compound 20 (9 g, 85%) as a liquid. [α]D = 56.1 (c = 0.5, CHCl₃)²; 1H NMR (CDCl₃, 300 MHz): δ 7.18 (2H, J = 2.9 Hz), 5.77-5.71 (m, 1H), 5.28 (dd, 2H, J = 10.7, 29.2 Hz), 4.59 (ABq, 2H, J = 6.8 Hz), 4.58-4.53 (m, 1H), 3.33 (s, 3H), 2.71-2.05 (m, 1H), 2.55-2.49 (m, 1H); 13C NMR (CDCl₃, 75 MHz): 202.0, 136.3, 118.0, 93.7, 72.0, 55.4, 48.7. IR (Neat): 2927, 1721, 2922, 1720, 1638, 1421, 1217, 1030 cm⁻¹.
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. Solvent was removed extracted with EtOAc. The organic layer was washed with water, brine and 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] D²⁺: (+) 3.1 (c = 1, CHCl₃); 'H 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) 2.84 (br, s, 1H), 2.01 (m, 1H), 0.87 (d, 3H, J = 6.9 Hz); IR (neat): 2960, 2855, 1709, 1611, 1513, 1248, 1091 cm⁻¹; EIMS: 231 (M++ 23).

To a solution of (Methyl) triphenylphosphonium iodide (22.2 g, 65% in dry CH₂Cl₂ (15 mL). After stirring for 2h 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, 1:9) to give an aldehyde 22(5.7 g, 85%) as a viscous liquid; [α] D²⁻: (-) 17.0 (c = 1, CHCl₃); 'H NMR (CDCl₃, 200 MHz): δ 7.67 (2d, 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 = 7.5 Hz); IR (neat): 2960, 2855, 1709, 1611, 1513, 1248, 1091 cm⁻¹; EIMS: 231 (M⁺ + 23).

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

(2R)-3-[(4-methoxybenzyl)oxy]-2-methylbutan-1-ol (24)

To a stirred solution of compound 23 (3.2 g, 15.53 mmol) in dry THF (15 mL) under N₂ atmosphere was added BH₄⁻, 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] D²⁻: (+) 3.1 (c = 1, CHCl₃); 'H NMR (CDCl₃, 200 MHz): δ 7.20 (2d, 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, 1035, 819 cm⁻¹; EIMS: 225 (M⁺ + 1).

1-methoxy-4-[(2R)-2-methyl-3-butenyl]oxy)methylbenzene (23)

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 TBDPSCI (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] D²⁻: (+) 17.0 (c = 1, CHCl₃); 'H 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 135.5, 134.7, 129.6, 129.4, 129, 127.5, 113.6, 75.5, 72.4, 62, 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⁺).

(2R)-4-[(1-tert-buty1)-(1-diphenylsilyl)oxy-2-methylbutan-1-ol (26)

To a stirred solution of compound 25 (3.8 g, 8.22mmol) in dry CH₂Cl₂ (15 mL) and water (2 mL) was added DDQ (2.24 g, 9.87 mmol) at room temperature. The reaction 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 26 (2.39 g, 85%) as a pure yellow oil; [α] D²⁻: (+) 6.8 (c = 1, CHCl₃); 'H NMR (CDCl₃, 400 MHz): δ 7.66 (m, 4H), 7.41-7.35 (m, 6H), 3.78-3.64 (m, 2H), 3.51-3.41 (m, 2H), 2.29 (brs, 2H), 1.88-1.77 (m, 1H), 1.67-1.56 (m, 1H), 1.53-1.41 (m, 1H), 1.05 (s, 9H), 0.91 (d, 3H, J = 6.7 Hz); IR (neat): 3349, 3062, 2938, 2868, 1468, 1428, 1106, 1003, 815, 702 cm⁻¹; EIMS: 343 (M⁺ + 1).

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To an ice-cooled solution of iodoxybenzoic acid (1.27 g, 4.54 mmol) in DMSO (5 mL) was added a solution of alcohol 30(1.2 g, 3.03 mmol) in dry CH$_2$Cl$_2$ (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 Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (EtOAc/hexane, 1:9) to give an aldehyde 30 (0.954 g, 80%) as a viscous liquid.; [α]$_D$ $^+$ 35 : (+) 25.6 ($c = 1$, CHCl$_3$); $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.64-7.59 (m, 4H), 7.38-7.29 (m, 6H), 6.69 (dd, 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, 1H), 2.16 (q, 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 (s, 3H, $J = 7.1$ Hz), 0.95 (d, 3H, $J = 6.1$ Hz); $^1$C NMR (CDCl$_3$, 75 MHz): δ 181.9, 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(3,4R)-6-[1-(tert-buty1)-1,1-diphenylsilyl]oxy-2-ethyl-4-methyl-2-hexenal(30)**

To a solution of the phosphonium salt S-II (1.94 g, 5.17 mmol) in dry THF (5 mL), NaH (0.225 g, 9.41 mmol) in dry THF (5 mL) was added over a cooled (0°C) suspension of 2-ethyl-3-methyl-2-hexenal(30) (1.6 g, 4.70 mmol) in dry THF (5 mL). After stirring for 1 h the reaction mixture was diluted with 5 mL of Et$_2$O and quenched by the slow addition of 4 mL of H$_2$O. The layers were separated, and the aqueous phase was extracted with two 10 mL portions of Et$_2$O. The organic extract was washed with brine solution, dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (EtOAc/hexane, 1:9) to afford a colorless liquid.; [α]$_D$ $^+$ 35 : (-) 6.9 ($c = 1$, CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz): δ 8.10 (s, 1H), 7.79 (dd, 4H, $J = 0.6$, 14.6 Hz), 7.41-3.1 (m, 6H), 6.08 (d, 1H, $J = 10.7$ Hz), 3.65-3.55 (m, 2H), 3.54-3.48 (m, 1H), 2.15 (q, 2H, $J = 7.8$, 15.6 Hz), 1.73-1.66 (m, 1H), 1.49-1.43 (m, 1H), 1.07 (d, 3H, $J = 5.8$ Hz), 1.03 (s, 9H), 0.96 (t, 3H, $J = 7.8$ Hz); $^1$C NMR (CDCl$_3$, 75 MHz): δ 181.9, 153.5, 140.7, 135.4, 133.5, 129.6, 126.7, 61.3, 39.8, 27.3, 26.7, 21.3, 19.13; IR (neat): 2960, 2831, 1726, 1146, 1106, 702 cm$^{-1}$; EIMS: 12 ($M^+$ $+$ 15Na$^+$).
A 250 ml flask equipped with a septum in, 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 18.5 mL (115 mmol) of (+)-α-pinene (neat) was added drop wise. After the mixture was stirred at 0°C for 1 h. ([(-)-Ipc,BH] separated as a white solid during this time) the flask was stored in a refrigerator at 0°C for 2 days.

To the (-)-Ipc,BH (solid, 50 mmol) was added neat olefin 32 (18.3 g, 75 mmol). The reaction mixture was stirred at -25°C for 1 h. The trialkyl borane was treated with 50 mL of 3N sodium hydroxide, 7.5 mL of 30% hydrogen peroxide and stirred at 25°C for 5 h. Compound was extracted with ether, dried over Na$_2$SO$_4$, and the ether was evaporated. The residue was filtered through silica gel (pet-ether-acetone 1:1) to give the crude lactone 35 (15.5 g, 80%). 

LDA was prepared by the addition of n-BuLi (1.6 mole solution in hexane, 27.1 mL, 43.4 mmol) to a 0°C cooled solution of DIPA (6.62 mL, 47 mmol) in dry THF (18 mL). After stirring at 0°C for 45 min, it was added to a solution of lactone 35 (10 g, 36.2 mmol) in dry THF (40 mL) at -78°C. After 1 h, the lithium enolate was generated and alkylated with ethyl iodide (8.7 mL, 108.6 mmol). Stirring was continued for further 2 h at -78°C and 2 h at room temperature and quenched with saturated ammonium chloride. The reaction mixture was extracted with ether, dried over anhydrous Na$_2$SO$_4$, evaporated the solvent and purified by column chromatography on silica gel. The 35 (23.0 g, 80%) was obtained as white solid.

To a solution of triol 9 (5.5 g, 17.7 mmol) in dry CH$_2$Cl$_2$ (40 mL), 2, 2-dimethoxy propane (16 mL, 123.9 mmol) and PTSA (6.62 mL, 47 mmol) in dry THF (18 mL). After stirring at 0°C for 4 h, the reaction mixture was filtered through Celite and then quenched with drop wise addition of 5% NaHCO$_3$ solution 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): δ 7.70–7.23 (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); 13C NMR (CDCl$_3$, 75 MHz): δ 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): 2949, 1730, 1212, 771 cm$^{-1}$; FAB Mass: m/z 305 (M$^+$+1).

**2 R ,3 R ,4 S, 5 R, 6 R )-7- (benzylxoy) -4-ethyl-6,8-dimethyl-1,3-dioxan-4-yl-1-methylpentan-1-ol (36)**

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 was then 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 vacuo and the residue was purified by column chromatography on silica gel column chromatography to afford the compound 9 (5.7 g, 80%) as a solid.
(2.2 g, 14.1 mmol) was added. The mixture was stirred at ambient temperature for 12 h. Sodium bicarbonate was added to neutralize PTSA and filtered. Removal of solvent and purification by silica gel column chromatography afforded the mono acetonide 37 (4.5 g, 54.7 mmol) was added slowly. It was stirred overnight at room temperature. The reaction mixture was diluted with DCM and washed with aqueous copper sulphate solution, water, and brine solution and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under vacuum and the residue was purified by column chromatography to afford the compound 37 (2.6 g, 80%); [α]$_D$= 1, CHCl$_3$; m/z 395 (M + +1); FAB mass: m/z 395 (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 ether and the aqueous phase extracted with ether. The organic layers were combined, washed once with water, brine, dried over anhydrous Na$_2$SO$_4$, 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. [a]$D^2$: $+2.7$ (c = 1.1, CHCl$_3$); $^1$H NMR (CDCl$_3$, 200 MHz): $8.45$ (br, OH), $3.93$ (dd, 1H, $J_{1H, J_{1H}} = 11.0, 3.0$ Hz), $3.67$ (s, 1H, $J = 2.7$ Hz), $3.71$ (dd, $1H, J_{1H, J_{1H}} = 9.1, 3.0$ Hz), $3.57$ (dd, $1H, J_{1H, J_{1H}} = 11.0, 4.3$ Hz), $3.15$ (br, OH), $2.08-2.00$ (m, 1H), $1.76-1.68$ (m, 1H), $1.62-1.55$ (m, 1H), $1.47-1.37$ (m, 1H), $1.26-1.16$ (m, 1H). $1.14$ (d, $3H, J_{1H, J_{1H}} = 7.0$ Hz), $0.97$ (d, $3H, J_{1H, J_{1H}} = 6.7$ Hz), $0.92$ (s, 9H), $0.89$ (t, $3H, J = 7.3$ Hz), $0.83$ (d, $3H, J = 7.0$ Hz) $0.14$ (s, 3H), $0.10$ (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $8.80, 79.7, 64.5, 40.1, 36.5, 35.6, 28.4, 25.8, 15.5, 15.2, 13.8, 12.2, $-4.2, -4.5$; IR (neat): $3413, 2959, 1024$ cm$^{-1}$. Mixture of above prepared aldehyde ($0.39$ g, $1.23$ mmol) and allylic bromide ($0.218$ g, $0.55$ mmol) was dissolved in dry CH$_2$Cl$_2$ ($5$ mL). The solution was allowed to warm to ambient temperature before an aqueous NaHCO$_3$ ($0.017$ mL, $0.15$ mmol) and CBr$_4$ ($0.554$ g, $1.67$ mmol) were added sequentially. After $15$ min, the solution was concentrated under vacuum, saturated with $10\%$ EtOAc/hexane, and filtered through Celite. Concentration under vacuum, followed by flash chromatography through silica gel ($1.9$ EtOAc: Hexanes) afforded allyl bromide ($0.268$ g, $93\%$). $^1$H NMR (CDCl$_3$, 200 MHz): $8.59$ (d, $1H, J = 9.9$ Hz), $3.98$ (d, $2H, J = 3.3$ Hz), $3.84-3.80$ (br, s, $1H$), $3.69$ (s, $1H, J = 2.7$ Hz), $3.55$ (d, $1H, J = 9.9$ Hz), $2.47-2.40$ (m, $1H$), $1.75$ (s, $3H$), $1.37-1.67$ (m, $1H$), $1.59-1.54$ (m, $1H$), $1.39-1.34$ (m, $1H$), $1.26-1.71$ (m, $1H$), $1.04$ (d, $3H, J = 7.1$ Hz), $0.98$ (d, $3H, J = 6.6$ Hz), $0.92$ (s, $9H$), $0.89$ (t, $3H, J = 7.1$ Hz), $0.721$ (d, $3H, J = 6.6$ Hz), $0.08$ (d, $6H, J = 19.3$ Hz).

Preparation of phosphonium salt (6)

Allyl bromide $46$ (0.1 g, 0.23 mmol) was dissolved in dry CH$_2$Cl$_2$ ($5$ mL) and cooled to $0^\circ$C. TPP ($0.365$ g, $1.39$ mmol), $2,6$-lutidine ($0.017$ mL, $0.15$ mmol) and CBr$_4$ ($0.554$ g, $1.67$ mmol) were added sequentially. After $15$ min, the solution was concentrated under vacuum, saturated with $10\%$ EtOAc/hexane, and filtered through Celite. Concentration under vacuum, followed by flash chromatography through silica gel ($1.9$ EtOAc: Hexanes) afforded allyl bromide $46$ ($0.268$ g, $93\%$). $^1$H NMR (CDCl$_3$, 200 MHz): $8.59$ (d, $1H, J = 9.9$ Hz), $3.98$ (d, $2H, J = 3.3$ Hz), $3.84-3.80$ (br, s, $1H$), $3.69$ (s, $1H, J = 2.7$ Hz), $3.55$ (d, $1H, J = 9.9$ Hz), $2.47-2.40$ (m, $1H$), $1.75$ (s, $3H$), $1.37-1.67$ (m, $1H$), $1.59-1.54$ (m, $1H$), $1.39-1.34$ (m, $1H$), $1.26-1.71$ (m, $1H$), $1.04$ (d, $3H, J = 7.1$ Hz), $0.98$ (d, $3H, J = 6.6$ Hz), $0.92$ (s, $9H$), $0.89$ (t, $3H, J = 7.1$ Hz), $0.721$ (d, $3H, J = 6.6$ Hz), $0.08$ (d, $6H, J = 19.3$ Hz).

Preparation of phosphonium salt (6)

Allyl bromide $46$ (0.1 g, 0.23 mmol) was dissolved in dry acetonitrile ($5$ mL) and tributylphosphine ($0.071$ g, $0.35$ 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,4Z)-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 ($0.12$ g, $0.78$ mmol) in dry CH$_2$Cl$_2$ ($3$ 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 Na$_2$SO$_4$ and concentrated invacuo. The crude product was purified by column chromatography on silica gel (EtOAc/hexane, $0.59:5$) to give an aldehyde ($47.0.083$ g, $85\%$) as a viscous liquid; $^1$H NMR (CDCl$_3$, 300 MHz): $6.96$ (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); $^{13}$C NMR (CDCl$_3$, 75 MHz): $8.200, 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 $175$ (M$^+$ + $23$).
A solution of n-BuLi (1.6 M, 0.131 mL, 0.209 mmol) was added to a solution of DMSO (0.064), in dry toluene (0.55mL) at room temperature, then the whole was stirred for 45 min. A solution of phosphonium 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 dimsyl carbanion at -78°C to 0°C overnight. The reaction mixture was pured 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 (0.67 g, 60% yield); [α]D 20.3 (c = 0.5, CHCl₃); 4H 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, J = 7.1, 14.5 Hz), 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, J = 0.7 Hz), 0.73 (d, 3H, J = 6.9 Hz), 0.08 (s, 3H), 0.06 (s, 3H); ¹³C NMR (CDCl₃, 75 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, 1639, 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**