Attempts towards the synthesis of mupirocin-H

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Received 06-18-2016  Accepted 04-16-2017  Published on line 04-29-2017

Abstract

The stereoselective synthesis of segments C1-C6 (3), C7-C12 (4) of mupirocin-H has been achieved. The synthetic procedure for the C1-C6 segment includes the zinc mediated allyl Grignard reaction with R-glyceraldehyde, Swern oxidation/Witting olefination reactions and followed by Sharpless asymmetric epoxidation. The C7-C12 segment was synthesized using again Sharpless asymmetric epoxidation on mono PMB protected 2-butene-1,4-diol, followed by regioselective opening of this epoxide with trimethyl aluminium. Both segments C1-C6 (3) and C7-C12 (4) possesses the five new stereogenic centers along with trans-olefin, but in various attempts condensation of 3 and 4 segments to give C-C bond forming parent segment (2) not affirmed, hence this work constitutes the synthesis of fragments C1-C6 (3) and C7-C12 (4) of mupirocin-H.

Keywords: Mupirocin-H, Sharpless asymmetric epoxidation, Wittig-olefination, D-mannitol

DOI: https://doi.org/10.24820/ark.5550190.p009.744
Introduction

Mupirocin is a polyketide, found to be possess a wider spectrum of antibacterial activity against both gram-positive, -negative bacteria, including methicillin-resistant staphylococcus aureus (MRSA) and it is used clinically for the treatment of bacterial skin infections.\(^1\) It is a mixture of pseudomonic acids produced by Pseudomonas fluorescens, a soil isolate reported to possess antibacterial activity as early as 1887,\(^2,3\) while the mixture of pseudomonic acids was found to be the active component in the 1960s,\(^4\) the major constituent was characterized later and named pseudomonic acid A (mupirocin).\(^5,6\) It is prescribed for treating skin infections such as cuts, burn wounds, candidiasis and impetigo. Besides mupirocin inhibits the bacterial isoleucyl tRNA synthetase enzyme responsible for loading the amino acid isoleucine onto its cognate tRNA required for ribosomal protein synthesis. Aminoacyl tRNA synthetases belong to a super family of nucleotidyl transferase enzymes related to other ATP-binding proteins such as dehydrogenases and photolyase.\(^7,8\) Consequently, mupirocin-H, is a novel metabolite belongs to the family of mupirocin and it is resulted mutation of the β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) synthase encoding mup H gene in Pseudomonas fluorescens and providing in vivo evidence for the roles of mup H and cognate genes found in several “AT-less” and other bacterial PKS gene clusters responsible for the biosynthesis of diverse metabolites containing acetate/propionate derived side chains, as well as possess anti bacterial activity akin mupirocin.\(^3,9,10\) Moreover, Mupirocin-H consisting of six stereogenic centers and one trans-olefinic bond, the structure of mupirocin-H was determined by extensive analysis spectroscopic data and has been confirmed by recent total syntheses.\(^10-15\)

![Structure of mupirocin and monic acids](image)

**Figure 1.** Structure of mupirocin and monic acids.

The amenable biological importance and fascinating structure of the mupirocin-H attracted the attention of chemists for the total synthesis. To date, five total synthesis of mupirocin-H were reported, sequentially are in 2011, the Chakraborty group reported the first enantioselective total synthesis of mupirocin-H in 19 steps with 5% overall yield by utilising D-glucose as the chiral source and Julia-Kocienski reaction for construction of the E-olefinic bond.\(^12\) In 2012 the Willis group also reported a convergent total synthesis of mupirocin H in 11 steps with 6.9% overall yield using a functionalized lactone transformation strategy.\(^10\) In 2014, She et al. have reported the total synthesis in 7 steps with 39% overall yield by utilizing Suzuki-Miyaura coupling reaction as
key step.\textsuperscript{14} Again in 2014, T. Sim and co-worker reported the concise synthesis of mupirocin-H in 17 steps with 10.1\% overall yield by using Grubbs reaction as key step.\textsuperscript{15}

In present work our goal is to target the synthesis of mupirocin-H. In a convergent synthesis, the target molecule mupirocin H 1 was divided into two fragments C1-C6 (3) and C7-C12 (4). Both the fragments are synthesized from commercially available starting materials. The detailed retro synthetic approach for the synthesis of mupirocin-H is depicted in scheme 1.

**Results and Discussion**

The retro synthetic analysis revealed that the target compound 1 (Scheme 1) could be obtained from alcohol 2, which on further conversion of resulting primary alcohol to methyl/C5-hydroxy protection/selective deprotection MOM ether, followed by oxidation to carboxylic acid and subsequent lactonization with deprotected C4-PMB ether. Compound 2 in turn could be obtained from two building blocks 3 and 4, while, epoxide 3 C-1 to C-6 segment could be obtained from (R)-glyceraldehyde derivative 5 (Scheme 2 & 3). Similarly, 4 C-7 to C-12 segment could be derived from allyl alcohol 20, which was derived from commercially available 2-butyne-1,4-diol (Scheme 4 & 5).

**Scheme 1.** Retro synthetic analysis of mupirocin-H.

**Synthesis of C-1 to C-6 segment (3).** Synthesis of fragment 3 is achieved as shown in Scheme 2. Allylation of (R)-Glyceraldehyde with allyl bromide in THF gave the isomeric mixture of compounds 5 and 5a.\textsuperscript{16} The major isomer 5 isolated by column chromatography and further treated with benzyl bromide and NaH in THF to give
the benzyl ether 7 in 94% yield. Then compound 7 was subjected to 70% aq. acetic acid at room temperature furnished diol 8 in 87% yield (Scheme 2). Diol 8 was selectively silylated using TBSCI and imidazole in dichloromethane at 0 °C to room temperature to give silyl ether 9 in 77% yield. Repeatedly, secondary alcohol in 9 was O-benzylated with ρ-methoxybenzyl bromide and NaH in THF to afford the PMB ether 10 in 91% yield. Dihydroxylation of terminal olefin of compound 10 in presence of OsO₄ in acetone, water (9:1) using NMO as cooxidant gave diol 11 in 62% yield. Then oxidative cleavage of diol 11 on reaction with NaIO₄ and saturated NaHCO₃ solution in CH₂Cl₂ furnished aldehyde 12, which on subsequent treatment with NaBH₄ in MeOH at 0 °C furnished alcohol 13 in 82% yield. Resulted alcohol 13 on reaction with MOMCl and DIPEA in CH₂Cl₂ at 0 °C afforded MOM ether 14 in 91% yield.

**Scheme 2. Synthesis of intermediate 15 of C-1 to C-6 segment.**

For the synthesis of one of the fragmet 3 from compound 14, first deprotected the TBS ether in compound 14 using TBAF in THF to give primary alcohol 15 in 85% yields. The obtained alcohol 15 was subjected for Swern oxidation in CH₂Cl₂ at -78 °C afforded aldehyde 16, which on subsequent Wittig olefination with (ethoxycarbonylmethylene)triphenyl phosphorane in benzene gave mixture of 17a and 17b in 1:19 ratio (75%). Then using column chromatography technique purified major isomer 17b on selective reduction of ester with LAH and AlCl₃ in ether at 0 °C furnished trans-allylic alcohol 18 in 78% yield (Scheme 3). The allylic alcohol 18 was subjected to enantioselective epoxidation under Sharpless asymmetric epoxidation reaction conditions using (+)-DIPT, Ti(i-OPr)₄ and cumene hydroperoxide at -20 °C furnished the desired chiral epoxide 3 in 70% yield. 

Reagents and conditions: a) Bn-Br, NaH, THF, RT, 6 h; b) 70% AcOH, RT, 12 h; c) TBS-Cl, Imidazole, CH₂Cl₂; d) PMB-Br, NaH, THF, RT, 6 h; e) OsO₄, NMO, Acetone,H₂O, 24 h; f) NaIO₄, sat.NaHCO₃, CH₂Cl₂; g) NaBH₄, MeOH, 0 °C, 2 h; h) MOM-Cl, DIPEA,DMAP, CH₂Cl₂, 12 h; i) TBAF, THF, 0 °C, 2 h.
Scheme 3. Synthesis of C-1 to C-6 segment 3.

Synthesis of C-7 to C-12 segment (4). To achieve the synthesis of fragment 4 with required stereochemistry, we have used the commercially available achiral 2-butyne-1,4-diol as starting material as shown in Scheme 4. Accordingly, 2-butyne-1,4-diol was treated with PMB-Br, NaH and TBAI in THF to give PMB-ether 19, which on further reaction with Red-Al in dry ether afforded the trans-alcohol 20 in 62% yield. Alcohol 20 was subjected to enantio selective epoxidation under Sharpless epoxidation reaction conditions using (+)-DIPT, Ti(i-OPr)_4 and cumene hydroperoxide at -20 °C furnished the chiral epoxide 21 in 69% yield. The newly generated chiral epoxide alcohol 21 on oxidation under Swern reaction conditions gave aldehyde 22, which on subsequent Wittig olefination with (ethoxy carbonylmethylene)triphenyl phosphorane in benzene afforded 6 and 6a in 9:1 ratio (72%). Epoxy ester 6 was treated with trimethylaluminium in CH_2Cl_2 at -40 °C to give regioselective compound 23 in 85% yield exclusively. Then, α,β-unsaturated ester 23 on selective reduction of ester with LAH and AlCl_3 in ether gave the diol 24 in 58% yield. The primary alcohol in 24 was selectively silylated using TBSCI and imidazole in CH_2Cl_2 to give silyl ether 25 in 82% yield.

Scheme 4. Synthesis of intermediate 24 of C-7 to C-12 segment.

Confirmation of newly generated stereocenter in compound 23, first deprotection of PMB ether in compound 25, followed by protection of resulted diol 27 with 2,2-dimethoxy propane and PPTS (cat.) in CH_2Cl_2 afforded 28 in 73% yield. The stereochemistry of 26 was established by ^1H NMR (300 MHz, CDCl_3) data of
compound 28, which reveals that the adjacent vicinal proton coupling constants ($J = 10.1$ Hz) of methyl and hydroxyl substituents are in anti-substitution pattern in 26.

For taking the intermediate compound 25 to the target compound 4, first protection of secondary alcohol (25) with benzyl bromide and NaH in THF at room temperature afforded the benzyl ether 26 in 76% yield (Scheme 5). Finally, desylation of 26 with TBAF in THF gave alcohol 29 in 88% yield, which on reaction with triphenylphosphine, and NaHCO$_3$ in CCl$_4$ at 80 °C afforded allyl halide 4 in 90% yield.

Scheme 5. Synthesis of C-7 to C-12 segment.

Attempts towards the synthesis of segment 2. In above obtained both segments C-1 to C-6, 3 (Scheme 3) and C-7 to C-12, 4 (Scheme 5) were further attempted to condense through epoxide opening procedure to furnish the main fragment 2 as shown in scheme 6. Hence the treatment of allyl halide 4 with Mg in ether at room temperature followed by reaction with 3 at -78 °C, few other attempts -40 °C, -20 °C and even at room temperature in dry ether/tetrahydrofuran reaction conditions were met with failure to furnish 2 (Scheme 6).$^{25,26}$

Scheme 6. Coupling of segments 3 and 4.

Conclusions
A route was developed for the synthesis of C1 to C6 (3), C7 to C12 (4) segments of mupirocin-H (1). In further attempts towards the synthesis of mupirocin-H 1 to form C-C bond forming main segment (2) by using both segments C1-C6 (3) and C7-C12 (4) was not affirmed. So this is a synthetic protocol for the synthesis of C1 to C6 segment (3), which has three chiral centers, and C7 to C12 segment (4), which has two chiral centers along with trans-olefin. Further work on the synthesis of mupirocin H (1) is in progress in our laboratories, with modified protocols.

**Experimental Section**

**General.** Analytical thin layer chromatography (TLC) was carried out using silica gel 60 F254 pre-coated plates. Visualization was accomplished with UV lamp or I₂ stain. All products were characterized by their NMR and HRMS spectra. The ¹H NMR (300 MHz) spectra were recorded on Bruker Avance spectrometer and ¹³C NMR (75 MHz) spectra were recorded on Bruker Avance spectrometers using TMS as an internal standard, chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. ESI, HRMS were recorded on ‘High Resolution QSTAR XL hybrid MS/MS system, Applied biosystems’ under Electron Spray Ionization conditions preparing sample solutions in MeOH. IR spectra were recorded on Perkin-Elmer Infrared-683 spectrometer.

(1S)-1-[(2R)-1,4-Dioxaspiro[4.5]dec-2-yl]-3-buten-1-ol (5). To a cooled (0 °C) solution of mannitol diacetonide (20 g, 58.47 mmol) in CH₂Cl₂ (100 mL), NaO₄ (25.02 g, 116.95 mmol) followed by sat. NaHCO₃ (8 mL) were added and stirred at room temperature for 5 h. Reaction mixture was dried (CaSO₄), filtered and evaporated under reduced pressure to give (R)-Glyceraldehyde (18 g) and used as such to next reaction. To a stirred and cooled (0 °C) mixture of (R)-Glyceraldehyde (18 g, 105.26 mmol) and dry Zinc (13.7 g, 210.50 mmol) in THF (100 mL), allyl bromide (10.7 mL, 126.30 mmol) was added very slowly for 15 min, followed by the addition of sat. NH₄Cl (72 mL) solution. After 6 h, reaction mixture was diluted with excess sat. NH₄Cl solution (50 mL) and extracted with ethyl acetate (2 x 100 mL). The organic layers were washed with water (2 x 20 mL), brine (20 mL), dried (CaSO₄), evaporated under reduced pressure and purified the residue by column chromatography (Silica gel, 60-120 mesh, 5% EtOAc in pet. ether) to furnish 5 (17.5 g, 78%) as a yellow liquid. [α]₀ +1.7 (c 2.5, CHCl₃); IR (neat): 2985, 2936, 2863, 1613, 1513 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 5.87-5.77 (m, 2H), 5.14-5.10 (m, 2H), 3.98-3.91 (m, 2H), 3.89-3.85 (m, 1H), 3.72-3.69 (m, 1H), 2.23-2.14 (m, 2H), 1.60-1.55 (m, 8H), 1.41-1.38 (m, 2H); ESIMS: 235 (M+ Na)+, 213 (M + H).

(2R)-2-[(1S)-1-(Benzyloxy)-3-butenyl]-1,4-dioxaspiro[4.5]decane (7). To a cooled (0 °C) solution of 5 (8.0 g, 54.8 mmol) in dry THF (40 mL), NaH (2.63 g, 109.6 mmol) was added, stirred for 30 min and treated with a solution of benzyll bromide (12.05 g, 60.28 mmol). After stirring at room temperature for 6 h, the reaction mixture was quenched with sat. NH₄Cl solution (8 mL) and extracted with ethyl acetate (2 x 40 mL). The organic layers were washed with water (2 x 10 mL), brine (10 mL), dried (CaSO₄), evaporated under reduced pressure and purified the residue by column chromatography (Silica gel, 60-120 mesh, 15% EtOAc in pet. ether) to furnish 7 (12.1 g, 83%) as a yellow liquid. [α]₀ +41.7 (c 1.5, CHCl₃); IR (neat): 2985, 2936, 2863, 1613, 1513 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.32-7.28 (m, 5H), 5.93-5.79 (m, 1H), 5.14-5.04 (m, 2H), 4.57 (q, J 11.33 Hz, 2H), 4.02-3.95 (m, 2H), 3.85-3.79 (m, 1H), 3.52 (q, J 5.28 Hz, 1H), 2.46-2.27 (m, 2H), 1.58-1.54 (m, 8H), 1.46-1.38 (s, 2H); ESIMS: 325 (M+ Na)+, 303 (M + H).
(2R,3S)-3-(Benzyloxy)-5-hexene-1,2-diol (8). A solution of 7 (9.12 g, 0.03 mmol) in aq. 70% acetic acid (50 mL) was stirred at room temperature for 12 h. After completion of reaction, it was quenched with NaHCO₃ and adjusted to pH 2-3. The reaction mixture was extracted with ethyl acetate (3 x 100 mL) and dried (Na₂SO₄). Evaporation of solvent under reduced pressure and purification of the residue by column chromatography (Silica gel, 60-120 mesh, 40% EtOAc in pet. ether) afforded 8 (5.76 g, 86%) as a yellow liquid. [α]D +42.9 (c 1.0, CHCl₃); IR (neat): 3456, 2990, 2942, 2863, 1613, 1513 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.32-7.24 (m, 5H), 5.93-5.79 (m, 1H), 5.14-5.04 (m, 2H), 4.57 (q, J 11.33 Hz, 2H), 4.02-3.95 (m, 2H), 3.85-3.79 (m, 1H), 3.52 (q, J 5.28 Hz, 1H), 2.46-2.27 (m, 2H), 1.58-1.54 (m, 8H), 1.46-1.38 (s, 2H); ESIMS: 245 (M+ Na)⁺, 223 (M + H).

(2R,3S)-3-(Benzyloxy)-1-[1-(tert-buty1),1,1-dimethylsilyloxy]-5-hexen-2-ol (9). To a cooled (0 °C) solution of 8 (1.8 g, 8.10 mmol) in CH₂Cl₂ (30 mL), imidazole (1.10 g, 16.21 mmol) was added. After 30 min TBS-Cl (1.21 g, 8.10 mmol) was added portion wise for 30 min and stirred at room temperature for 2 h. The reaction mixture was evaporated and purified by column chromatography (Silica gel, 60-120 mesh, 5% EtOAc in pet. ether) to give 9 (2.08 g, 76.7%) as a colorless liquid. [α]D +45.3 (c 1.0, CHCl₃); IR (neat): 3031, 2930, 2857, 1710, 1097 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 7.32-7.25 (m, 5H), 5.95-5.81 (m, 1H), 5.15-5.04 (m, 2H), 4.63 (d, J 12.08 Hz, 1H), 4.45 (d, J 12.08 Hz, 1H), 3.71 (t, J 6.04 Hz, 1H), 3.65-3.58 (m, 2H), 3.46 (q, J 6.04 Hz, 1H), 2.49-2.35 (m, 2H), 0.89 (s, 9H), 0.61 (s, 6H); ESIMS: 359 (M+ Na)⁺, 337 (M + H).

((2R,3S)-3-(Benzyloxy)-2-[1-(4-methoxybenzyl)oxy]-5-hexenyl)oxy)pentane-1,2-diol (10). To a cooled (0 °C) solution of 9 (5.93 g, 17.70 mmol) in dry THF (30 mL), NaH (1.22 g, 53.10 mmol) was added, stirred for 30 min and treated with a solution of MPMBr (4.22 g, 21.24 mmol) in dry THF (15 mL). After 6 h stirring at room temperature, the reaction mixture was quenched with sat. NH₄Cl solution (10 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layers were washed with water (2 x 10 mL), brine (10 mL) and dried (Na₂SO₄). Solvent was evaporated under reduced pressure and purified by column chromatography (Silica gel, 60-120 mesh, 2% EtOAc in pet. ether) to furnish 10 (7.35 g, 91.3%) as a yellow liquid. [α]D -17.7 (c 1.0, CHCl₃); IR (neat): 3394, 2929.6, 1718, 1612, 1456, 1247, 823 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.27-7.24 (m, 5H), 7.21 (d, J 8.3 Hz, 2H), 6.97 (dd, J 4.53, 8.3 Hz, 2H), 5.92-5.76 (m, 1H), 5.09-5.0 (m, 2H), 4.60 (d, J 11.3 Hz, 1H), 4.53 (s, 1H), 4.50 (d, J 12.8 Hz, 1H), 4.39 (s, 1H), 3.78 (s, 3H), 3.76-3.71 (m, 1H), 3.57 (q, J 5.28 Hz, 1H), 3.52-3.43 (m, 2H), 2.37 (t, J 6.7 Hz, 2H), 0.89 (s, 9H), 0.37 (s, 6H); ¹³C NMR (CDCl₃, 150 MHz) δ (ppm): 135.4, 129.3, 128.2, 127.8, 127.3, 116.8, 113.6, 80.4, 78.5, 72.3, 72.2, 62.8, 55.2, 34.9, 25.9, -5.3. ESIMS: 479 (M+ Na)⁺, 457 (M + H).

((4S,5R)-4-(Benzyloxy)-6-[1-(tert-buty1),1,1-dimethylsilyl]oxy-5-[4-methoxybenzyl]oxy)- hexane-1,2-diol (11). To the stirred solution of 10 (6.85 g, 15.05 mmol) in acetone, water (9:1; 30 mL) NMO (7.07 mL, 30.1 mmol) was added at room temperature followed by the addition of OsO₄ (2 mL) catalytic amount (which was covered by paper). After 12 h, reaction mixture was quenched with NaHSO₃ (5 g), acetone was removed and extracted the residue with ethyl acetate (2 x 50 mL). The organic layers were washed with water (2 x 10 mL), brine (10 mL), dried (Na₂SO₄), evaporated and purified the residue by column chromatography (Silica gel, 60-120 mesh, 30% EtOAc in pet. ether) to give 11 (4.6 g, 63%) as a liquid. [α]D +25.2 (c 1.0, CHCl₃); IR (neat): 3395, 2929, 2858, 1717, 1611, 1458, 1360, 1248, 824 cm⁻¹; ¹H NMR (CDCl₃) δ (ppm): 7.31-7.25 (m, 5H), 7.21 (d, J 8.68 Hz, 2H), 6.82 (d, J 8.68 Hz, 2H), 4.6-4.47 (m, 4H), 3.85-3.78 (m, 1H), 3.78 (s, 3H), 3.72-3.6 (m, 3H), 3.5-3.46 (m, 1H), 3.4-3.32 (m, 2H), 1.69-1.62 (m, 2H), 0.88 (s, 9H), 0.38 (s, 6H); ¹³C NMR (CDCl₃, 150 MHz) δ (ppm): 128.4, 128.1, 127.8, 113.7, 79.7, 78.9, 72.4, 69.3, 66.8, 62.5, 55.2, 32.9, 25.8, -5.4; ESIMS: 513 (M+ Na)⁺.

(3S,4R)-3-(Benzyloxy)-5-[1-(tert-buty1),1,1-dimethylsilyl]oxy-4-[4-methoxybenzyl] oxy]pentan-1-ol (13). To a cooled (0 °C) solution of 11 (4.61 g, 9.42 mmol) in CH₂Cl₂ (20 mL), NaO₃ (3.02 g, 14.14 mmol) followed by

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sat. NaHCO₃ (2 mL) were added and stirred at room temperature for 5 h. Reaction mixture was dried (Na₂SO₄), filtered and evaporated under reduced pressure gave aldehyde 12, which was directly used as such for the next step.

To a cooled (0 °C) solution of 12 (2.92 g, 6.37 mmol) in methanol (20 mL), NaBH₄ (0.5 g, 12.75 mmol) was added portion wise for 30 min and stirred at room temperature for 5 h. After that methanol was removed and extracted with ethyl acetate (2 x 30 mL). The organic layers were washed with water (2 x 10 mL), brine (10 mL), dried (Na₂SO₄), evaporated and purified the residue by column chromatography (Silica gel, 60-120 mesh, 20% EtOAc in pet. ether) to furnish 13 (2.28 g, 76%) as a colorless liquid. [α]D²⁵ -49.7 (c 1.1, CHCl₃); IR (neat): 3452, 2929, 2858, 1719, 1611, 1463, 1254, 838 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 7.32-7.26 (m, 5H), 7.2 (d, J 8.4 Hz, 2H), 6.79 (d, J 8.4 Hz 2H), 4.62 (d, J 10.98 Hz, 1H), 4.59 (s, 1H), 4.57 (s, 1H), 4.49 (d, J 11.35 Hz, 1H), 3.78 (s, 3H), 3.78-3.74 (m, 1H), 3.71-3.6 (m, 5H), 1.89-1.73 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (CDCl₃, 150 MHz) δ (ppm): 129.4, 128.4, 127.9, 127.7, 113.6, 79.9, 77.9, 72.5, 71.9, 62.6, 60.2, 55.2, 32.3, 25.8, -5.4; ESIMS: 483 (M+ Na)⁺, 461 (M + H)⁺.

[(2R,3S)-3-(Benzyloxy)-2-[(4-methoxybenzyl)oxy]-5-(methoxymethoxy)pentyl]oxy[(tert-butyldimethyl silane 14). To a cooled (0 °C) solution of 13 (2.6 g, 5.65 mmol) in CH₂Cl₂ (15 mL), DIPEA (5.87 mL, 33.91 mmol) and MOM-Cl (0.91 mL, 11.3 mmol) were added sequentially and stirred at room temperature for 6 h. The reaction mixture was evaporated and purified the residue by column chromatography (Silica gel, 60-120 mesh, 5% EtOAc in pet. ether) to afford 14 (2.57 g, 92%) as a yellow liquid. [α]D²⁵ –27.1 (c 0.6, CHCl₃); IR (neat): 3446, 2929, 2858, 1720, 1609, 1460, 1101, 837 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 7.29-7.26 (m, 5H), 7.2 (d, J 8.78 Hz, 2H), 6.79 (d, J 8.78 Hz, 2H), 4.62-4.56 (m, 3H), 4.52-4.45 (m, 3H), 3.77 (s, 3H), 3.73-3.67 (m, 3H), 3.58 (t, J 6.83 Hz, 3H), 3.28 (s, 3H), 1.84-1.79 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (CDCl₃, 150 MHz) δ (ppm): 129.3, 128.2, 127.9, 127.5, 113.6, 96.4, 96.1, 80.6, 76.3, 72.4, 72.3, 64.5, 62.9, 55.18, 55.13, 30.7, 29.7, 25.9, -5.3; ESIMS: 527 (M+ Na)⁺, 522 (M + NH₄)⁺.

(2R,3S)-3-(Benzyloxy)-2-[(4-methoxybenzyl)oxy]-5-(methoxymethoxy)pentan-1-ol (15). To a cooled (0 °C) solution of 14 (2.75 g, 5.45 mmol) in dry THF (15 mL) under nitrogen atmosphere, TBAF (6.54 mL, 6.54 mmol) was added and stirred for 3 h. After completion of reaction, reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 x 50 mL). Organic layers were washed with water (2 x 10 mL), brine (10 mL), dried (Na₂SO₄), evaporated and purified the residue by column chromatography (Silica gel, 60-120 mesh, 25% EtOAc in pet. ether) furnished 15 (1.8 g, 85%) as a liquid. [α]D₀ -15.4 (c 1.0, CHCl₃); IR (neat): 3451, 2929, 2857, 2102, 1722, 1612, 1360, 1041, 777 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 7.31-7.29 (m, 5H), 7.21 (d, J 8.5 Hz, 2H), 6.81 (d, J 8.3 Hz, 2H), 4.65 (d, J 11.2 Hz, 1H), 4.62-4.49 (m, 5H), 3.78 (s, 3H), 3.77-3.73 (m, 1H), 3.70-3.69 (m, 2H), 3.60 (t, J 5.85 Hz, 2H), 3.50 (q, J 4.8 Hz, 1H), 3.30 (s, 3H), 1.86-1.81 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz) δ (ppm): 129.4, 128.3, 127.9, 127.7, 113.8, 96.4, 80.6, 76.4, 72.9, 71.8, 64.2, 61.3, 55.2, 31.5; ESIMS: 413 (M+ Na)⁺, 391 (M + H)⁺.

Methyl(E,4R,5S)-5-(4-methoxybenzyl)oxy-7-(methoxymethoxy)-2-epctenoate (17). To a solution of oxalyl chloride (1.19 g, 9.42 mmol) in dry CH₂Cl₂ (5 mL) at -78 °C, dry DMSO (1.46 g, 18.84 mmol) was added drop wise and stirred for 20 min. A solution of 15 (2.45 g, 6.28 mmol) in dry CH₂Cl₂ (10 mL) was added and stirred for 2 h at -78 °C. It was quenched with Et₃N (3.8 g, 37.69 mmol) and diluted with CH₂Cl₂ (30 mL). The reaction mixture was washed with water (10 mL), brine (10 mL), dried (Na₂SO₄) and evaporated to furnish the corresponding aldehyde 16.

The aldehyde 16 (2.43 g, 6.26 mmol) was dissolved in benzene (30 mL) and treated with (methoxycarbonylmethylene)triphenyl phosphorane (2.51 g, 7.51 mmol) at reflux temperature. After 2 h, solvent was evaporated and purified the residue by column chromatography (Silica gel, 60-120 mesh, 10%
EtOAc in pet. ether) to furnish 17 (E:Z/19:1) (2.1 g, 75.5%) as a yellow liquid. **E isomer:** [α]_D -144.6 (c 1.0, CHCl₃); IR (neat): 3446, 2932, 1722, 1612, 1512, 1448, 1386, 1164, 1037 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.29-7.24 (m, 5H), 7.18 (d, J 8.68 Hz, 2H), 6.90 (dd, J 6.04, 12.3 Hz, 1H), 6.80 (d, J 8.6 Hz, 2H), 6.04 (d, J 15.5 Hz, 1H), 4.60 (d, J 7.22 Hz, 1H), 4.58 (d, J 10.2 Hz, 1H), 4.52-4.44 (m, 3H), 4.37 (d, J 11.7 Hz, 1H), 4.05-4.01 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.72-3.65 (m, 1H), 3.55 (t, J 5.6 Hz, 2H), 3.27 (s, 3H), 1.76 (q, J 6.42 Hz, 2H); ¹³C NMR (CDCl₃, 150 MHz) δ (ppm): 145.6, 129.3, 128.3, 127.8, 127.6, 123.2, 113.7, 96.4, 79.6, 78.0, 72.9, 64.1, 55.2, 55.1, 51.6, 31.2; HRMS m/z [M+Na]+ found 467.2055; calculated 467.2045 for C₂₅H₃₂O₃Na. **Z isomer:** [α]_D -58.0 (c 1.2, CHCl₃); IR (neat): 2939, 1721, 1649, 1612, 1513, 1447, 1299, 1196, 1041 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.31-7.21 (m, 5H), 7.18 (d, J 8.68 Hz, 2H), 6.76 (d, J 8.68 Hz, 2H), 6.26 (dd, J 8.68, 11.07 Hz, 1H), 5.91 (d, J 11.7 Hz, 1H), 5.29 (d, J 8.3 Hz, 1H), 4.73 (d, J 11.7 Hz, 1H), 4.57-4.39 (m, 6H), 3.77 (s, 3H), 3.73-3.70 (m, 2H), 3.70 (s, 3H), 3.56-3.51 (m, 2H), 3.25 (s, 3H), 1.87-1.77 (m, 1H), 1.72-1.64 (m, 1H); ESIMS: 462 (M⁺NH₄)⁺, 467 (M⁺Na)⁺.

**(E,4R,5S)-5-(Benzyl oxy)-4-[(4-methoxybenzyl)oxy]-7-(methoxymethoxy)-2-hepten-1-ol (18).** To the suspension of lithium aluminium hydride (LAH)(0.16 g, 4.22 mmol) in dry ether (5 mL) under nitrogen atmosphere at 0 °C, AlCl₃ (0.18 g, 1.40 mmol) in dry ether (3 mL) was added and stirred for 30 min. A solution of 17b (1.25 g, 2.81 mmol) in dry ether (5 mL) was added at the same temperature and stirred for an additional 1 h. Reaction mixture was quenched with sat. NH₄Cl (5 mL) solution, filtered through sintered funnel, dried (Na₂SO₄), evaporated and purified the residue by column chromatography (Silica gel, 60-120 mesh, 20% EtOAc in pet. ether) to give 18 (1.0 g, 78%) as a liquid. [α]_D -25.0 -82.2 (c 1.0, CHCl₃); IR (neat): 34450, 2929, 2855, 1460, 1032 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.28-7.27 (m, 5H), 7.21 (d, J 8.7 Hz, 2H), 6.80 (d, J 8.7 Hz, 2H), 5.82 (tt, J 4.9 Hz, 1H), 5.68 (dd, J 7.55, 13.4 Hz, 1H), 4.60 (d, J 11.7 Hz, 1H), 4.50-4.46 (m, 4H), 4.33 (d, J 11.7 Hz, 1H), 4.12 (d, J 4.9 Hz, 2H), 3.80 (s, 3H), 3.80 (dd, J 3.4, 3.7 Hz, 1H), 3.7-3.64 (m, 1H), 3.56 (t, 2H), 3.30 (s, 3H), 1.8-1.71 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz) δ (ppm): 133.8, 129.2, 128.5, 128.2, 127.9, 127.5, 113.6, 96.4, 81.2, 78.3, 72.9, 70.0, 64.4, 62.9, 55.2, 31.4; HRMS m/z [M+Na]+ found 439.2103; calculated 439.2096 for C₂₅H₃₂O₃Na.

**(2S,3R)-3-[(1S,2S)-2-(Benzyl oxy)-1-[(4-methoxybenzyl)oxy]-4-(methoxymethoxy)butyl]- oxiran-2-yl methanol (3).** To a stirred solution of (+)-DIPT (0.12 g, 0.50 mmol) in CH₂Cl₂ (5 mL) at -20 °C containing MS 4 Å (0.4 g), sequentially Ti(OiPr)₄ (0.119 g, 0.42 mmol) and tBHP (0.14 mL, 0.42 mmol) were added and stirred for 20 min. A solution of 18 (0.35 g, 0.84 mmol) in CH₂Cl₂ (5 mL) was added and stirred for 15 h at -20 °C. The reaction mixture was quenched with 10% NaOH solution (0.5 g in 5 mL brine) and stirred for 3 h and filtered. The organic layers were dried (Na₂SO₄), evaporated and the residue obtained was purified by column chromatography (Silica gel, 60-120 mesh, 30% EtOAc in pet. ether) to afford 3 (0.25 g, 70%) as a colorless liquid. [α]_D -54.9 (c 0.4, CHCl₃); IR (neat): 3422, 3063, 2978, 2929, 2870, 1605, 1453 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.28-7.26 (m, 5H), 7.18 (d, J 8.7 Hz, 2H), 6.8 (d, J 8.3 Hz, 2H), 4.61 (d, J 11.7 Hz, 1H), 4.84-4.47 (m, 5H), 3.77 (s, 3H), 3.72 (m, 1H), 3.6-3.57 (m, 3H), 3.53 (m, 1H), 3.30 (s, 3H), 3.07 (m, 1H), 1.9-1.83 (m, 1H); ¹³C NMR (CDCl₃, 150 MHz) δ (ppm): 129.2, 128.3, 127.9, 127.6, 113.7, 96.5, 78.0, 72.7, 72.5, 64.3, 61.4, 55.9, 55.2, 54.7, 31.0; HRMS m/z [M+Na]+ found 455.2052; calculated 455.2045 for C₂₅H₃₂O₇Na.

**4-[(4-Methoxy benzyl)oxy]-2-buten-1-ol (19).** To a cooled (0 °C) solution of 2-buten-1,4-diol (9.0 g, 104.4 mmol) in dry THF (200 mL), NaH (2.76 g, 114.9 mmol) and TBAI (3.64 g, 10.44 mmol) were added, stirred for 30 min and treated with a solution of MPM-Br (20.7 g, 104.9 mmol) in dry THF (100 mL) for 12 h at room temperature. The reaction mixture was quenched with sat. NH₄Cl solution (20 mL) and extracted with ethyl acetate (2 x 100 mL). The organic layers were washed with water (2 x 50 mL), brine (10 mL), dried (Na₂SO₄), evaporated under reduced pressure and purified the residue by column chromatography (Silica gel, 60-120
(E)-4-[[4-Methoxybenzoyl]oxy]-2-buten-1-ol (20). To a solution of 19 (6.5 g, 0.03 mmol) in dry ether (30 mL), NaAlH4(OCH2CH2OMe)2 (12.74 mL, 0.06 mmol, solution in toluene) was added dropwise at 0 °C and stirred for 2 h at the same temperature. The reaction mixture was quenched with sat. NH4Cl solution (8 mL) and extracted with ethyl acetate (2 x 50 mL). Organic layers were washed with water (10 mL), brine (10 mL), dried (Na2SO4) and evaporated. The residue was purified by column chromatography (Silica gel, 60-120 mesh, 30% EtOAc in pet. ether) to afford 20 (4.78 g, 73%) as a light yellow liquid. IR (neat): 3453, 2929, 2859, 1611, 1512, 1458, 1301, 823 cm−1; 1H NMR (CDCl3, 400 MHz) δ (ppm): 7.21 (d, J 8.85 Hz, 2H), 6.82 (d, J 8.49 Hz, 2H), 4.48 (s, 2H), 4.26-4.25 (m, 2H), 4.12-4.11 (m, 2H), 3.78 (s, 3H), 2.09-2.03 (s, 1H); ESIMS: 229 (M+ Na)+, 224 (M + NH4)+.

[(2S,3S)-3-[[4-Methoxybenzoyl]oxy]methylloxiran-2-yl]methanol (21). To a stirred solution of (+)-DIPT (0.94 g, 4.03 mmol) in CH2Cl2 (10 mL) at -20 °C containing MS 4 Å (0.4 g), sequentially Ti(OiPr)4 (1.14 g, 4.03 mmol) and cumenehydroperoxide (2.59 g, 16.82 mmol) were added and stirred for 20 min. A solution of 20 (4.2 g, 20.19 mmol) in CH2Cl2 (20 mL) was added and stirred for an additional 6 h at -20 °C. The reaction mixture was worked up as described for 3 and the residue was purified by column chromatography (Silica gel, 60-120 mesh, 30% EtOAc in pet. ether) to furnish 21 (3.12 g, 69%) as a yellow liquid. [α]D20 +31.1 (c 0.75, CHCl3); IR (neat): 3454, 2932, 1513, 1248, 1036, 915 cm−1; 1H NMR (CDCl3, 300 MHz) δ (ppm): 7.19 (d, J 8.68 Hz, 2H), 6.80 (d, J 8.68 Hz, 2H), 4.45 (q, J 11.70 Hz, 2H), 3.84 (d, J 12.46 Hz, 1H), 3.78 (s, 3H), 3.63 (dd, J 5.73, 11.70 Hz, 1H), 3.62-3.55 (m, 1H), 3.46 (dd, J 7.4, 11.33 Hz, 1H), 3.16-3.12 (m, 1H), 3.02-3.00 (m, 1H); ESIMS: 247 (M+ Na)+, 242 (M + NH4)+.

Methyl (E,4R,5R)-5-hydroxy-6-[[4-methoxybenzoyl]oxy]-4-methyl-2-hexenoate (23). To a stirred solution of 6 (2.35 g, 8.45 mmol) in CH2Cl2 (100 mL) under nitrogen atmosphere at -40 °C, 3M Me3Al (42.3 mL, 85.5 mmol) solution was added. After 10 min, water (0.91 mL, 50.7 mmol) was added very slowly and stirred additionally at the same temperature for 2 h. The reaction mixture was quenched with sat. NH4Cl (10 mL) solution, filtered through sintered funnel, dried (Na2SO4), evaporated under reduced pressure and purified the residue by column chromatography (Silica gel, 60-120 mesh, 12% EtOAc in pet. ether) to give 23 (2.11 g, 85%) as a liquid. [α]D20 +50.8 (c 3.65, CHCl3); IR (neat): 3446, 2932, 1723, 1611, 1514, 1452, 1387, 1164, 919, 756 cm−1; 1H NMR (CDCl3, 500 MHz) δ (ppm): 7.19 (d, J 8.78 Hz, 2H), 6.96 (dd, J 7.8, 15.6 Hz, 1H), 6.82 (d, 2H), 5.79 (d, J 15.6 Hz, 1H), 4.44 (s, 2H), 3.79 (s, 3H), 3.71 (s, 3H), 3.69-3.66 (m, 2H), 3.42 (dd, J 3.9, 9.7 Hz, 1H), 3.31 (dd, J 6.83, 8.78 Hz, 2H), 2.45 (q, J 6.83 Hz, 1H), 1.09 (d, J 6.83 Hz, 3H); 13C NMR (CDCl3, 150 MHz) δ (ppm): 150.4, 129.6, 129.3, 121.2, 113.6, 73.0, 71.9, 55.1, 51.3, 39.4, 15.6; HRMS m/z [2M+Na]+ found 611.2752; calculated 611.2773 for C39H40O5Na.

(E,4S,5R)-6-[[4-Methoxybenzoyl]oxy]-4-methyl-2-hexene-1,5-diol (24). To a suspension of LAH (0.25 g, 6.63 mmol) in dry ether (3 mL) under nitrogen atmosphere at 0 °C, AlCl3 (0.29 g, 2.21 mmol) in dry ether (3 mL) was added and stirred for 30 min. A solution of 23 (1.3 g, 4.42 mmol) in dry ether (5 mL) was added at the same temperature and continued stirring for 1 h. Reaction mixture was quenched with sat. NH4Cl solution (5 mL), filtered through sintered funnel, dried (Na2SO4), evaporated and purified the residue by column chromatography (Silica gel, 60-120 mesh, 35% EtOAc in pet. ether) gave 24 (0.68 g, 58%) as a liquid. [α]D20 +22.2 (c 0.6, CHCl3); IR (neat): 3450, 2929, 1448, 922, 739 cm−1; 1H NMR (CDCl3, 300 MHz) δ (ppm): 7.17 (d, J 9.06 Hz, 2H), 6.83 (d, J 8.3 Hz, 2H), 5.64-5.62 (m, 2H), 4.43 (s, 3H), 4.03 (d, J 3.77 Hz, 2H), 3.79 (s, 3H), 3.59-3.54 (m, 1H), 3.42 (dd, J 3.02, 9.06 Hz, 1H), 3.37-3.27 (m, 1H), 2.34-2.25 (m, 1H), 0.99 (d, J 7.55 Hz, 3H); 13C NMR (CDCl3, 150
Methyl (E)-3-((2S,3R)-3-[[4-methoxybenzyl]oxy]methylloxiran-2-yl)-2-propenoate (6). To a solution of oxalyl chloride (2.61 g, 20.75 mmol) in dry CH₂Cl₂ (10 mL) at -78 °C, dry DMSO (3.23 mL, 41.51 mmol) was added dropwise and stirred for 20 min. A solution of 21 (3.1 g, 13.83 mmol) in dry CH₂Cl₂ (15 mL) was added and stirred for 2 h at -78 °C. It was quenched with Et₃N (8.38 g, 83.03 mmol) and diluted with CH₂Cl₂ (30 mL). The reaction mixture was washed with water (10 mL), brine (10mL), dried (Na₂SO₄) and evaporated to furnish the corresponding aldehyde 22.

The aldehyde 22 (3.0 g, 13.51 mmol) was dissolved in benzene (40 mL) and treated with (methoxycarbonylmethylene)triphenyl phosphorane (5.41 g, 16.21 mmol) at reflux temperature. After 2 h, solvent was evaporated and purified the residue by column chromatography (Silica gel, 60-120 mesh, 10% EtOAc in pet. ether) to furnish 6 (E:Z:9:1) (2.71 g, 72%) as a yellow liquid. E-isomer: [α]D -21.5 (c 0.45, CHCl₃); IR (neat): 3480, 2926, 2854, 1721, 1654, 1513, 1460, 1252, 938 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.18 (d, J 8.3 Hz, 2H), 6.83 (d, J 8.6 Hz, 2H), 6.65 (dd, J 7.17, 15.86 Hz, 1H), 6.10 (d, J 15.8 Hz, 1H), 4.51-4.42 (m, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 3.65 (dd, J 3.39, 11.33 Hz, 1H), 3.53 (dd, J 4.53, 11.3 Hz, 1H), 3.46 (d, J 6.79 Hz, 1H), 3.06 (br s, 1H); ¹³C NMR (CDCl₃, 150 MHz) δ (ppm): 144.0, 129.4, 123.7, 113.8, 73.09, 68.7, 59.5, 55.2, 53.6, 51.7; ESIMS: 301 (M+ Na)⁺, 296 (M + NH₄)⁺, 579 (2M+ Na)⁺. Z-isomer: [α]D +115.3 (c 1.0, CHCl₃); IR (neat): 3033, 2932, 2889, 1725, 1664 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 7.23 (d, J 8.87 Hz, 2H), 6.81 (d, J 8.68 Hz, 2H), 5.96 (d, J 11.52 Hz, 1H), 5.78 (dd, J 8.12, 11.52 Hz, 1H), 4.50 (q, J 11.7 Hz, 2H), 4.40-4.37 (m, 1H), 3.75-3.73 (m, 1H), 3.73 (s, 3H), 3.45 (dd, J 5.85, 11.7 Hz, 1H), 3.08-3.04 (m, 1H); ESIMS: 301 (M+ Na)⁺, 296 (M + NH₄)⁺.

(2R,3R,4E)-6-[1-(tert.-Butyl)-1,1-dimethylylsilyloxy-1-[[4-methoxybenzyl]oxy]-3-methyl-4-hexen-2-ol (25). To a cooled (0 °C) solution of 24 (0.8 g, 3.0 mmol) in CH₂Cl₂ (15 mL), imidazole (0.41 g, 6.0 mmol) was added. After 30 min, TBS-Cl (0.45 g, 3.0 mmol) was added portionwise for 30 min and stirred at room temperature for 2 h. The reaction mixture was quenched with Et₃N (25 mL) and diluted with CH₂Cl₂ (50 mL), imidazole (0.41 g, 6.0 mmol) was added. After 30 min, TBS-Cl (0.45 g, 3.0 mmol) was added portionwise for 30 min and stirred at room temperature for 2 h. The reaction mixture was quenched with sat. NH₄Cl solution (5 mL) and extracted with ethyl acetate (2 x 20 mL). The organic layers were washed with water (2 x 10 mL), brine (10 mL), dried (Na₂SO₄), evaporated under reduced pressure and purified the residue by column chromatography (Silica gel, 60-120 mesh, 5% EtOAc in pet. ether) to afford 25 (0.9 g, 82%) as a colorless liquid. [α]D +3.62 (c 0.4, CHCl₃); IR (neat): 3033, 2929, 2855, 1460, 1032 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 7.2 (d, J 7.8 Hz, 2H), 6.8 (d, J 8.3 Hz, 2H), 5.61 (dd, J 7.8, 15.6 Hz, 1H, 5.52 (tt, J 4.87 Hz, 1H), 4.44 (s, 2H), 4.10 (d, J 4.87 Hz, 2H), 3.79 (s, 3H), 3.59-3.57 (br s, 1H), 3.43 (dd, J 2.92 Hz, 10.7 Hz, 1H), 3.33-3.30 (m, 1H), 2.33-2.29 (m, 1H), 1.01 (d, J 6.83 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (CDCl₃, 150 MHz) δ (ppm): 133.9, 130.0, 129.3, 113.7, 73.7, 72.9, 72.2, 63.3, 55.2, 39.2, 16.6; ESIMS: 403 (M+ Na)⁺, 381 (M + H).
(2R,3R,4E)-6-[1-(tert-Butyl)-1,1-dimethylsilyl]oxy-3-methyl-4-hexene-1,2-diol (27). To a solution of 25 (0.13 g, 0.35 mmol) in aq. CH$_2$Cl$_2$ (2 mL, 19:1), DDQ (0.12 g, 0.53 mmol) was added and stirred at room temperature for 1 h. The reaction mixture was quenched with sat. NaHCO$_3$ solution (1 mL), filtered and washed with CH$_2$Cl$_2$ (10 mL). The filtrate was washed with water (3 mL), brine (3 mL), dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (Silica gel, 60-120 mesh, 30% EtOAc in pet. ether) to furnish 27 (0.06 g, 74%) as a yellow liquid. [α]$_D$ +13.2 (c 0.15, CHCl$_3$); IR (neat): 3442, 2922, 2853, 1630, 1126, 835 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm): 5.64-5.52 (m, 2H), 4.1 (d, J 5.3 Hz, 2H), 3.67-3.50 (m, 2H), 3.40-3.38 (m, 1H), 2.51-2.44 (m, 1H), 1.02 (d, J 6.79 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 6H); ESIMS: 283 (M+ Na)$^+$.  

(4R)-4-[(1R,2E)-4-[1-(tert-Butyl)-1,1-dimethylsilyl]oxy-1-methyl-2-butyl]-2,2-dimethyl-1,3-dioxolane (28). A solution of 27 (0.06 g, 0.002 mmol) in CH$_2$Cl$_2$ (2 mL) was treated with 2,2-dimethoxypropane (0.05 g, 0.005 mmol) and stirred in presence of PPTS (cat.) at room temperature for 3 h. The reaction mixture was evaporated under reduced pressure and purified the residue by column chromatography (Silica gel, 60-120 mesh, 5% EtOAc in pet. ether) to furnish 28 (0.05 g, 73%) as a yellow liquid. [α]$_D$ +18.5 (c 0.2, CHCl$_3$); IR (neat): 3067, 2931, 2857, 1456 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm): 5.65-5.48 (m, 2H), 4.12 (d, J 4.53 Hz, 2H), 3.94-3.87 (m, 2H), 3.56 (t, J 10.19 Hz, 1H), 2.35-2.26 (m, 1H), 1.25 (s, 6H), 1.01 (d, J 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ESIMS: 323 (M+ Na)$^+$, 318 (M + NH$_4$)$^+$.  

(E,4R,5R)-5-(Benzyloxy)-6-[[4-methoxy benzyl]oxy]-4-methyl-2-hexen-1-ol (29). To a cooled (0 °C) solution of 26 (0.35 g, 0.77 mmol) in dry THF (3 mL) under nitrogen atmosphere, TBAF (0.77 mL, 0.77 mmol) was added and stirred for 3 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x 50 mL). Organic layers were washed with water (2 x 5 mL), brine (5 mL), dried (Na$_2$SO$_4$) and purified by column chromatography (60-120 Silica gel, 25% EtOAc in pet. ether) to afford 29 (0.23 g, 88%) as a liquid. [α]$_D$ +11.2 (c 0.4, CHCl$_3$); IR (neat): 3444, 3065, 2927, 1661, 1452 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.29-7.24 (m, 5H), 7.17 (d, J 8.30 Hz, 2H), 6.83 (d, J 8.68 Hz, 2H), 5.67-5.50 (m, 2H), 4.61 (q, J 11.70 Hz, 2H), 4.39 (q, J 11.70 Hz, 2H), 4.00 (d, J 4.53 Hz, 2H), 3.79 (s, 3H), 3.48-3.41 (m, 3H), 2.49-2.43 (m, 1H), 1.03 (d, J 6.79 Hz, 3H); ESIMS: 379 (M+ Na)$^+$, 374 (M + NH$_4$)$^+$.  

4(E,4R,5R)-5-(Benzyloxy)-1-chloro-6-[[4-methoxybenzyl]oxy]-4-methyl-2-hexene (4). To a stirred solution of 29 (0.11 g, 0.32 mmol) in CCl$_4$ (2 mL), Ph$_3$P (0.17 g, 0.65 mmol) and NaHCO$_3$ (cat.) were added and heated at reflux for 3 h. The reaction mixture was evaporated and purified the residue by column chromatography (Silica gel, 60-120 mesh, 5% EtOAc in pet. ether) to afford 4 (0.11 g, 90%) as a liquid. [α]$_D$ +24.3 (c 0.33, CHCl$_3$); IR (neat): 3063, 2928, 2864, 1606, 1451 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ (ppm): 7.31-7.24 (m, 5H), 7.21 (d, J 8.30 Hz, 2H), 6.80 (d, J 8.30 Hz, 2H), 4.56 (q, J 12.08 Hz, 2H), 4.42 (s, 2H), 3.88-3.85 (m, 2H), 3.79 (s, 3H), 3.52-3.50 (m, 1H), 3.37-3.26 (m, 2H), 1.82-1.68 (m, 1H), 0.89 (d, J 6.79 Hz, 3H); ESIMS: 397 (M+ Na)$^+$, 392 (M + NH$_4$)$^+$.  

Acknowledgements  

The authors BSB and TP are thankful to UGC, New Delhi, India, for the award of research fellowships.  

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