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Attempts towards the synthesis of mupirocin-H

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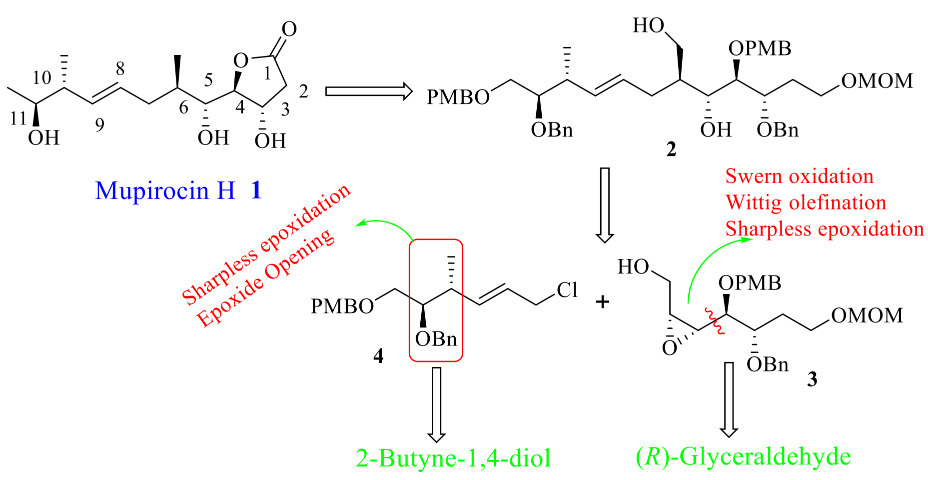
Abstract

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

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 **1**, 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]

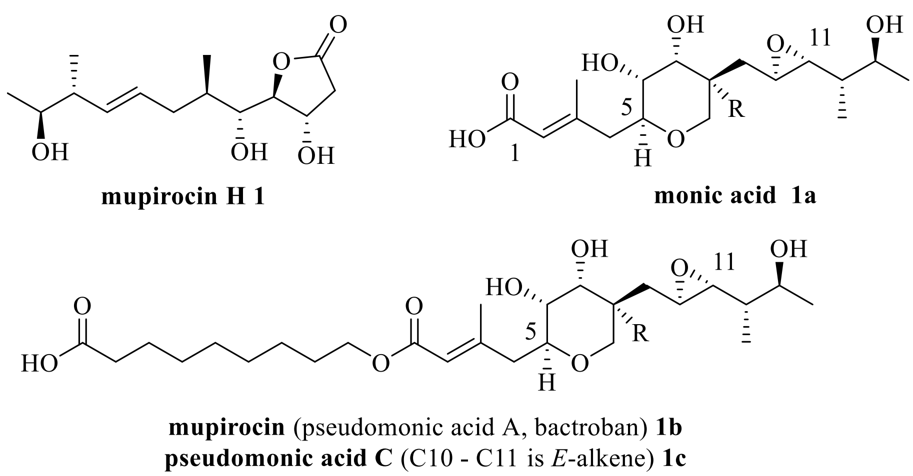


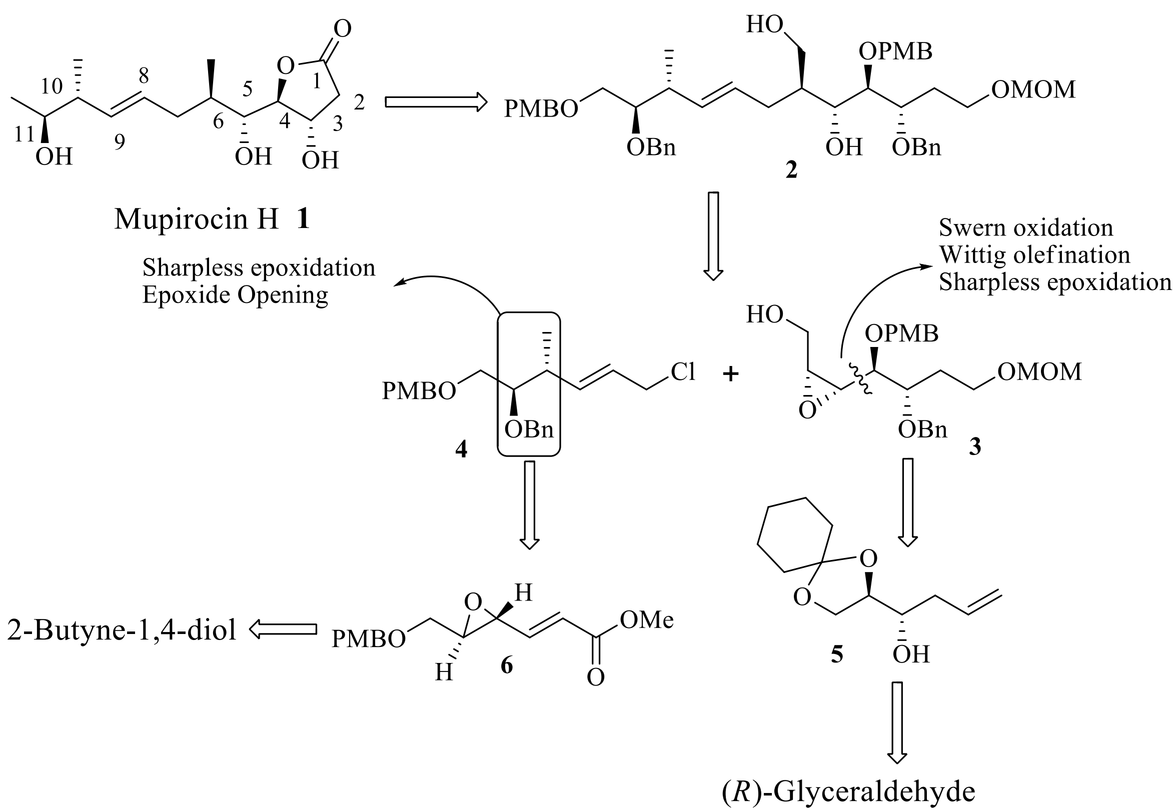
Figure 1. Structure of mupirocin and monic acids.

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.[14] Again in 2014, T. Sim and co-worker reported the consise synthesis of mupirocin-H in 17 steps with 10.1% overall yield by using Grubbs reaction as key step.[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 devided into two fragments C1-C6 (**3**) and C-7-C12 (**4**). Both the fragments are synthesized from commericially available starting materials.The detailed retro synthetic approach for the synthesis of mupirocin-H is depicted in scheme 1.

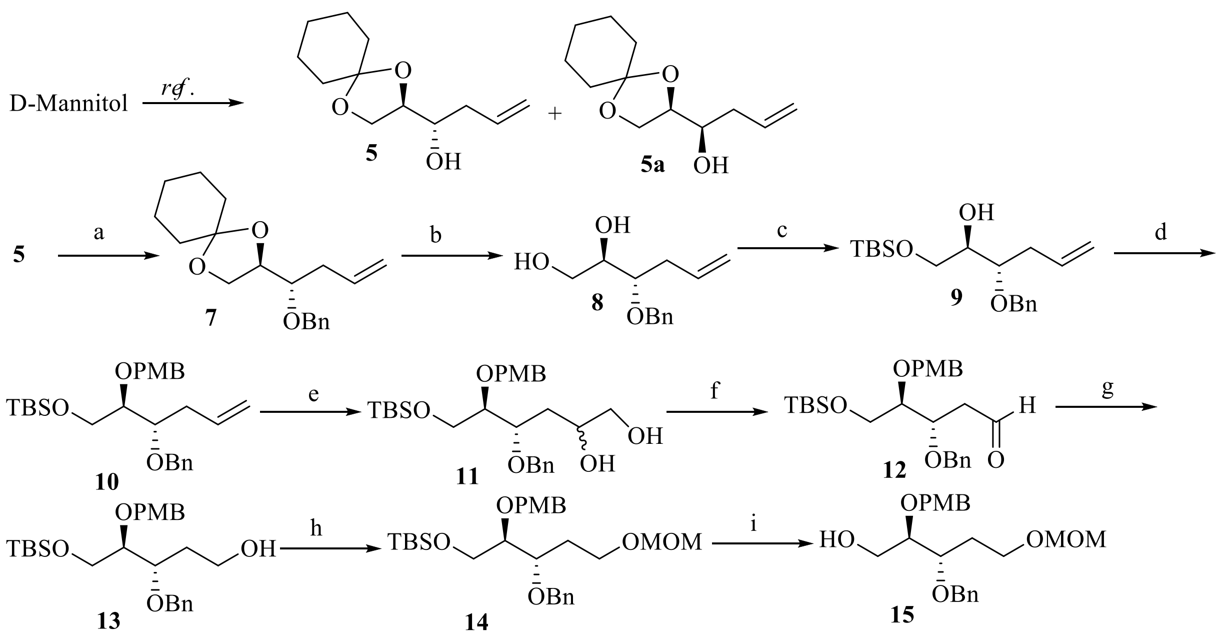
Results and Discussion

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.

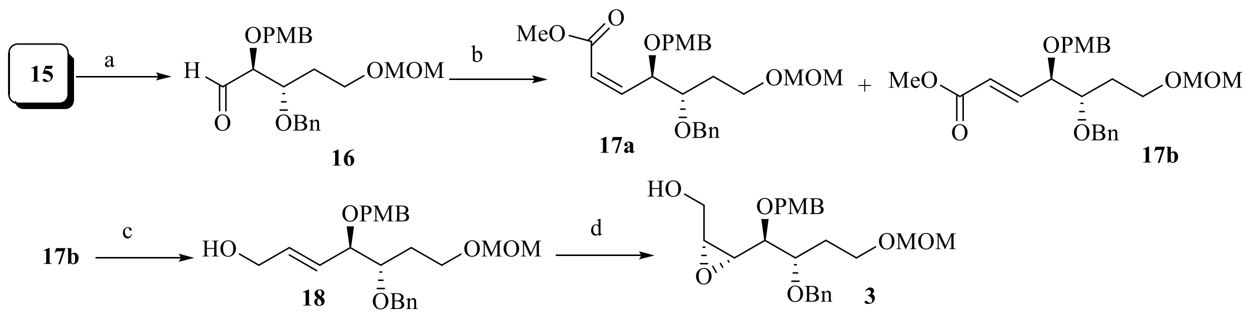
Synthesis of C-1 to C-6 segment (3). Synthesis of fragment **3** is achieved as shown in Scheme 2. Allylation of (*R*)-Glyceraldehyde with allyl bromide in THF gave the isomeric mixture of compounds **5** and **5a**.[16] The major isomer **5** isolated by colomn chromatography and further treated with 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 silylted using TBSCl 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 *p*-methoxybenzyl bromide and NaH in THF to afford the PMB ether **10** in 91% yield. Dihydroxylation of terminal olefine of compound **10** in presence of OsO_4 in acetone, water (9:1) using NMO as cooxidant gave diol **11** in 62% yield.[17] Then oxidative cleavage of diol **11** on reaction with $NaIO_4$ and saturated $NaHCO_3$ solution in CH_2Cl_2 furnished aldehyde **12**, which on subsequent treatment with $NaBH_4$ in MeOH at 0 °C furnished alcohol **13** in 82% yield. Resulted alcohol **13** on reaction with MOMCl and DIPEA in CH_2Cl_2 at 0 °C afforded MOM ether **14** in 91% yield.



Reagents and conditions: a) Bn-Br, NaH, THF, RT, 6 h; b) 70% AcOH, RT, 12 h; c) TBS-Cl, Imidazole, CH_2Cl_2; d) PMB-Br, NaH, THF, RT, 6 h; e) OsO_4, NMO, Acetone,H_2O, 24 h; f) $NaIO_4$, sat.$NaHCO_3$, CH_2Cl_2; g) $NaBH_4$, MeOH, 0 °C, 2 h; h) MOM-Cl, DIPEA,DMAP, CH_2Cl_2, 12 h; i) TBAF, THF, 0 °C, 2 h.

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

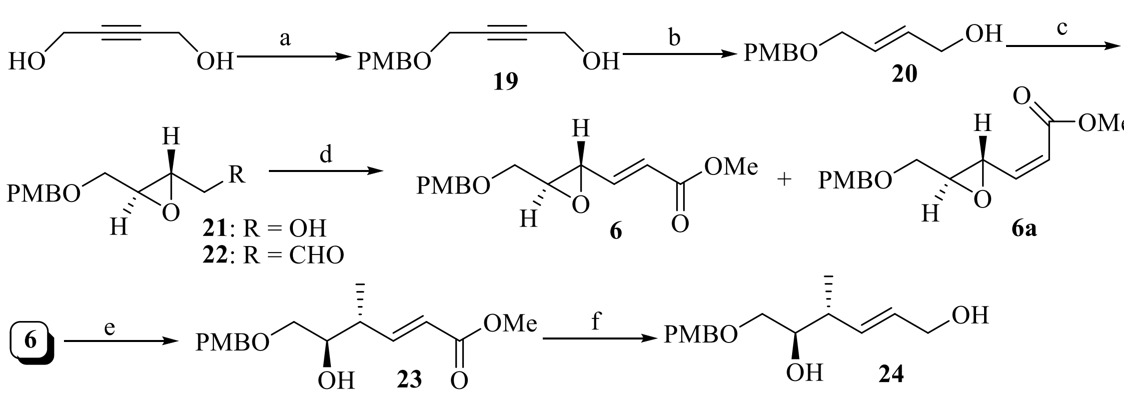
For the synthesis of one of the fragmet **3** from compound **14**, first deprotected the TBS ether in compound **14** using TBAF in THF to give primary alcohol **15** in 85% yields. The obtained alcohol **15** was subjected for Swern oxidation in CH_2Cl_2 at -78 °C afforded aldehyde **16**,[18,19] which on subsequent Wittig olefination with (ethoxycarbonylmethylene)triphenyl phosphorane in benzene gave mixture of **17a** and **17b** in 1:19 ratio (75%).[20,21,22] Then using colomn chromatography technique purified major isomer **17b** on selective reduction of ester with LAH and $AlCl_3$ 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.[23]



Reagents and conditions: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 2 h; b) Benzene, Ph_3P=CHCOOMe, 90 °C, 3 h; c) LAH, $AlCl_3$, Ether, 0 °C, 1 h; d) (+)-DIPT, Ti(iPrO)$_4$, CHP, CH_2Cl_2, -20 °C, 72 h.

Scheme 3. Synthesis of C-1 to C-6 segment **3**.

Synthesis of C-7 to C-12 segment (4). To acieve the synthesis of fragment **4** with required stereochemistry, we have used the commercially available achiral 2-butyn-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.[23] The newly generated chiral epoxide alcohol **21** on oxidation under Swern reaction conditions[18,19] gave aldehyde **22**, which on subsequent Wittig olefination with (ethoxycarbonylmethylene)triphenyl phosphorane in benzene afforded **6** and **6a** in 9:1 ratio (72%).[20,21,22] Epoxy ester **6** was treated with trimethylaluminium in CH_2Cl_2 at -40 °C to give regioselective compound **23** in 85% yield an exclusively.[24] 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 TBSCl and imidazole in CH_2Cl_2 to give silyl ether **25** in 82% yield.

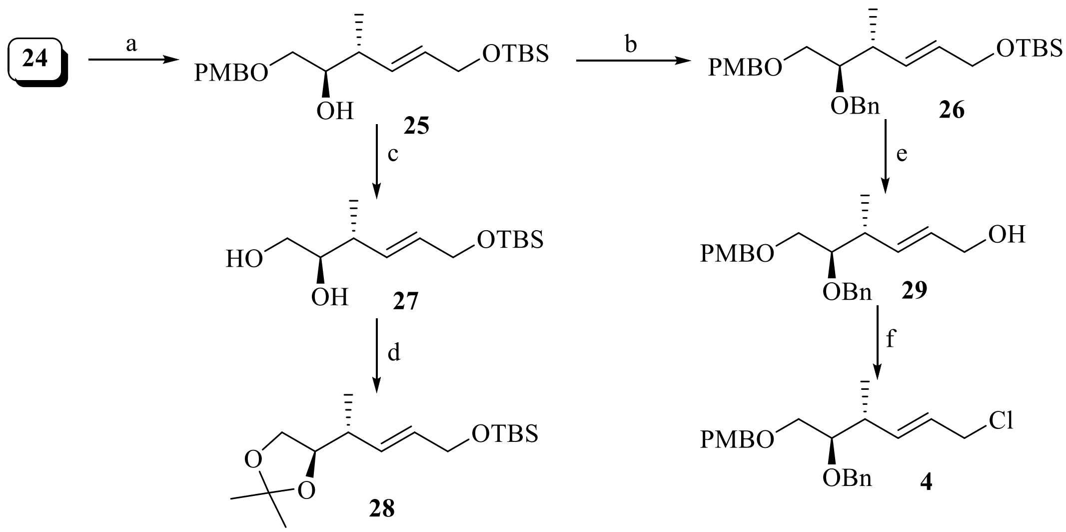


Reagents and Conditions: a) PMB-Br, NaH, TBAI ,THF, 12 h; b) Red-Al, ether, 0 °C, 2 h; c) (+) DIPT, Ti(O^{i}Pr)$_4$, CHP, CH_2Cl_2, -20 °C, 12 h; d) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 2 h (ii) Benzene, Ph_3P=CHCOOMe, 90 °C, 3 h; e) $Al(CH_3)_3$, H_2O, CH_2Cl_2, -40 °C, 2 h; f) LAH, $AlCl_3$, Ether, 0 °C, 1 h.

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 ^{1}H 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.**

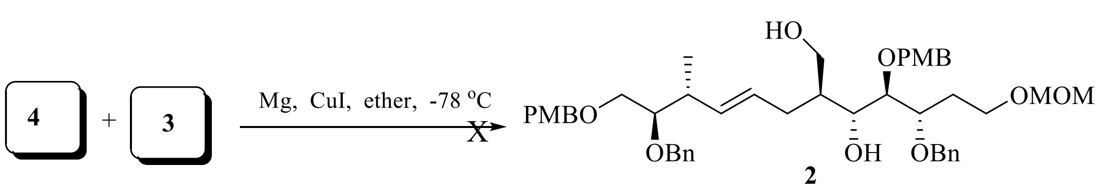
For taking the intermediate compound **25** to the target compound **4**, first protection of secondary alcohol (**25**) with benzyl bromide and NaH in THF at room temperature afforded the benzyl ether **26** in 76% yield (Scheme 5). Finally, desylilation of **26** with TBAF in THF gave alcohol **29** in 88% yield, which on reaction with triphenylphosphine, and $NaHCO_3$ in CCl_4 at 80 °C afforded allyl halide **4** in 90% yield.



Reagents and Conditions: a) TBS-Cl, Imidazole, CH_2Cl_2; b) Bn-Br, NaH, THF, 8 h; c) DDQ, CH_2Cl_2, H_2O(19:1), 10 min; d) 2,2-DMP, PPTS, CH_2Cl_2, 2 h; e) TBAF, THF, 2 h; f) TPP,CCl_4, $NaHCO_3$, 80 °C, 3 h.

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 I_2 stain. All products were characterized by their NMR and HRMS spectra. The ^{1}H NMR (300 MHz) spectra were recorded on Bruker Avance spectrometer and ^{13}C 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.

(1*S*)-1-[(2*R*)-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 CH_2Cl_2 (100 mL), $NaIO_4$ (25.02 g, 116.95 mmol) followed by sat. $NaHCO_3$ (8 mL) were added and stirred at room temperature for 5 h. Reaction mixture was dried (Na_2SO_4), 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. NH_4Cl (72 mL) solution. After 6 h, reaction mixture was diluted with excess sat. NH_4Cl 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 (Na_2SO_4), 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. $[\alpha]_D$ +1.7 (*c* 2.5, $CHCl_3$); IR (neat): 2985, 2936, 2863, 1613, 1513 cm^{-1}; ^{1}H NMR ($CDCl_3$, 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).

(2*R*)-2-[(1*S*)-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 benzyl bromide (12.05 g, 60.28 mmol). After stirring at room temperature for 6 h, the reaction mixture was quenched with sat. NH_4Cl 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 (Na_2SO_4), 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. $[\alpha]_D$ +41.7 (*c* 1.5, $CHCl_3$); IR (neat): 2985, 2936, 2863, 1613, 1513 cm^{-1}; ^{1}H NMR ($CDCl_3$, 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: 325 (M+ Na)$^+$, 303 (M + H).

(2*R*,3*S*)-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 temperatature for 12 h. After completion of reaction, it was quenched with $NaHCO_3$ and adjusted to pH 2-3. The reaction mixture was extracted with ethyl acetate (3 x 100 mL) and dried (Na_2SO_4). 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. $[\alpha]_D$ +42.9 (*c* 1.0, $CHCl_3$); IR (neat): 3456, 2990, 2942, 2863, 1613, 1513 cm^{-1}; ^1H NMR ($CDCl_3$, 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).

(2*R*,3*S*)-3-(Benzyloxy)-1-[1-(*tert.*-butyl)-1,1-dimethylsilyl]oxy-5-hexen-2-ol (9). To a cooled (0 °C) solution of **8** (1.8 g, 8.10 mmol) in CH_2Cl_2 (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 the residue 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. $[\alpha]_D$ +45.3 (*c* 1.0, $CHCl_3$); IR (neat): 3031, 2930, 2857, 1710, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 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).

((2*R*,3*S*)-3-(Benzyloxy)-2-[(4-methoxybenzyl)oxy]-5-hexenyloxy)(*tert*-butyl) dimethylsilane (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. NH_4Cl 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 (Na_2SO_4). Solvent was evaporated under reduced pressure and purified the residue 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. $[\alpha]_D$ -17.7 (*c* 1.0, $CHCl_3$); IR (neat): 3394, 2929.6, 1718, 1612, 1456, 1247, 823 cm^{-1}; ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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).

(4*S*,5*R*)-4-(Benzyloxy)-6-[1-(*tert.*-butyl)-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 OsO_4 (2 mL) catalytic amount (which was covered by carbon paper). After 12 h, reaction mixture was quenched with $NaHSO_3$ (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 (Na_2SO_4), evaporated and purified the residue by colomn chromatography (Silica gel, 60-120 mesh, 30% EtOAc in pet. ether) to gave **11** (4.6 g, 63%) as a liquid. $[\alpha]_D^{25}$ -32.9 (*c* 1.0, $CHCl_3$); IR (neat): 3395, 2929, 2858, 1717, 1611, 1458, 1360, 1248, 824 cm^{-1}; ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$, 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 $(M+ Na)^+$.

(3*S*,4*R*)-3-(Benzyloxy)-5-[1-(*tert.*-butyl)-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 CH_2Cl_2 (20 mL), $NaIO_4$ (3.02 g, 14.14 mmol) followed by sat. $NaHCO_3$ (2 mL) were added and stirred at room temperature for 5 h. Reaction mixture was dried (Na_2SO_4), 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), $NaBH_4$ (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 (Na_2SO_4), 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. $[\alpha]_D^{25}$ -49.7 (*c* 1.1, $CHCl_3$); IR (neat): 3452, 2929, 2858, 1719, 1611, 1463, 1254, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.32-7.26 (m, 5H), 7.2 (d, *J* 8.42 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); ^{13}C NMR ($CDCl_3$, 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).

[(2*R*,3*S*)-3-(Benzyloxy)-2-[(4-methoxybenzyl)oxy]-5-(methoxymethoxy)pentyl]oxy(*tert*-butyl)dimethyl silane (14). To a cooled (0 °C) solution of **13** (2.6 g, 5.65 mmol) in CH_2Cl_2 (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. $[\alpha]_D^{25}$ -27.1 (*c* 0.6, $CHCl_3$); IR (neat): 3446, 2929, 2858, 1720, 1609, 1460, 1101, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $(M + NH_4)^+$.

(2*R*,3*S*)-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 (Na_2SO_4), evaporated and purified the residue by colomn chromatography (Silica gel, 60-120 mesh, 25% EtOAc in pet. ether) furnished **15** (1.8 g, 85%) as a liquid. $[\alpha]_D$ -15.4 (*c* 1.0, $CHCl_3$); IR (neat): 3451, 2929, 2857, 2102, 1722, 1612, 1514, 1360, 1041, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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*,4*R*,5*S*)-5-(benzyloxy)-4-[(4-methoxybenzyl)oxy]-7-(methoxymethoxy)-2-eptenoate (17). To a solution of oxalyl chloride (1.19 g, 9.42 mmol) in dry CH_2Cl_2 (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 CH_2Cl_2 (10 mL) was added and stirred for 2 h at -78 °C. It was quenched with Et_3N (3.8 g, 37.69 mmol) and diluted with CH_2Cl_2 (30 mL). The reaction mixture was washed with water (10 mL), brine (10mL), dried (Na_2SO_4) 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:** $[\alpha]_D$ -144.6 (*c* 1.0, $CHCl_3$); IR (neat): 3446, 2932, 1722, 1612, 1512, 1448, 1386, 1164, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{25}H_{32}O_7Na$. **Z isomer:** $[\alpha]_D$ –58.0 (*c* 1.2, $CHCl_3$); IR (neat): 2939, 1721, 1649, 1612, 1513, 1447, 1299, 1196, 1041 cm^{-1};^{1}H NMR ($CDCl_3$, 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), 3.77-3.70 (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 $(M+NH_4)^+$, 467 $(M+ Na)^+$.

(*E*,4*R*,5*S*)-5-(Benzyloxy)-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, $AlCl_3$ (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. NH_4Cl (5 mL) solution, filtered through sintered funnel, dried (Na_2SO_4), 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. $[\alpha]_D^{25}$ -82.2 (*c* 1.0, $CHCl_3$); IR (neat): 34450, 2929, 2855, 1460, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{24}H_{32}O_6Na$.

(2*S*,3*R*)-3-[(1*S*,2*S*)-2-(Benzyloxy)-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 CH_2Cl_2 (5 mL) at -20 °C containing MS 4 Å (0.4 g), sequentially $Ti(O^iPr)_4$ (0.119 g, 0.42 mmol) and *t*BHP (0.14 mL, 0.42 mmol) were added and stirred for 20 min. A solution of **18** (0.35 g, 0.84 mmol) in CH_2Cl_2 (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 (Na_2SO_4), 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. $[\alpha]_D^{25}$ -54.9 (*c* 0.4, $CHCl_3$); IR (neat): 3422, 3063, 2978, 2929, 2870, 1605, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$, 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), 4.53-4.47 (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); ^{13}C NMR ($CDCl_3$, 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 $C_{24}H_{32}O_7Na$.

4-[(4-Methoxy benzyl)oxy]-2-butyn-1-ol (19). To a cooled (0 °C) solution of 2-butyn-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. NH_4Cl 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 (Na_2SO_4), evaporated under reduced pressure and purified the residue by column chromatography (Silica gel, 60-120 mesh, 25% EtOAc in pet. ether) to furnish **19** (13.01 g, 62%) as a yellow liquid. IR (neat): 3438, 2926, 2857, 2109, 1456 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.20 (d, *J* 8.49 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 $(M + NH_4)^+$.

(*E*)-4-[(4-Methoxybenzyl)oxy]-2-buten-1-ol (20). To a solution of **19** (6.5 g, 0.03 mmol) in dry ether (30 mL), $NaAlH_2(OCH_2CH_2OMe)_2$ (12.74 mL, 0.06 mmol, solution in toulene) was added dropwise at 0 °C and stirred for 2 h at the same temperature. The reaction mixture was quenched with sat. NH_4Cl solution (8 mL) and extracted with ethyl acetate (2 x 50 mL). Organic layers were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (Silica gel, 60-120 mesh, 30% EtOAc in pet. ether) afforded **20** (4.78 g, 73%) as a light yellow liquid. IR (neat): 3453, 2929, 2859, 1611, 1512, 1458, 1301, 823 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.21 (d, *J* 8.85 Hz, 2H), 6.82 (d, *J* 8.22 Hz, 2H), 5.86-5.75 (m, 1H), 4.48-4.41 (m, 1H), 4.41 (s, 2H), 4.10 (d, *J* 5.06 Hz, 1H), 3.95 (d, *J* 5.06 Hz, 1H), 3.78-3.66 (m, 2H), 3.78 (s, 3H); ESIMS: 231 $(M+ Na)^+$, 226 $(M + NH_4)^+$.

((2*S*,3*S*)-3-[(4-Methoxybenzyl)oxy]methyloxiran-2-yl)methanol (21). To a stirred solution of (+)-DIPT (0.94 g, 4.03 mmol) in CH_2Cl_2 (10 mL) at -20 °C containing MS 4 Å (0.4 g), sequentially $Ti(O^iPr)_4$ (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 CH_2Cl_2 (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 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. $[\alpha]_D^{25}$ -31.1 (*c* 0.75, $CHCl_3$); IR (neat): 3454, 2932, 1513, 1248, 1036, 915 cm^{-1}; ^{1}H NMR ($CDCl_3$, 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 $(M + NH_4)^+$.

Methyl (*E*,4*R*,5*R*)-5-hydroxy-6-[(4-methoxybenzyl)oxy]-4-methyl-2-hexenoate(23). To a stirred solution of **6** (2.35 g, 8.45 mmol) in CH_2Cl_2 (100 mL) under nitrogen atmosphere at -40 °C, 3M Me_3Al (42.3 mL, 84.5 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. NH_4Cl (10 mL) solution, filtered through sintered funnel, dried (Na_2SO_4), evaporated under reduced pressure and purified the residue by colomn chromatography (Silica gel, 60-120 mesh, 12% EtOAc in pet. ether) to give **23** (2.11 g, 85%) as a liquid. $[\alpha]_D$ +50.8 (*c* 3.65, $CHCl_3$); IR (neat): 3446, 2932, 1723, 1611, 1514, 1452, 1387, 1164, 919, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{39}H_{40}O_5Na$.

(*E*,4*S*,5*R*)-6-[(4-Methoxybenzyl)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, $AlCl_3$ (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. NH_4Cl solution (5 mL), filtered through sintered funnel, dried (Na_2SO_4), 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. $[\alpha]_D$ +22.2 (*c* 0.6, $CHCl_3$); IR (neat): 3450, 2929, 1448, 922, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 150

MHz) δ (ppm): 133.9, 130.05, 129.3, 113.8, 73.7, 72.9, 72.2, 63.4, 63.4, 55.2, 39.3, 16.6; HRMS *m/z* $[M+Na]^+$ found 289.1429; calculated 289.1415 for $C_{15}H_{22}O_4Na$.

Methyl (*E*)-3-((2*S*,3*S*)-3-[(4-methoxybenzyl)oxy]methyloxiran-2-yl)-2-propenoate (6). To a solution of oxalyl chloride (2.61 g, 20.75 mmol) in dry CH_2Cl_2 (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 CH_2Cl_2 (15 mL) was added and stirred for 2 h at -78 ^{0}C. It was quenched with Et_3N (8.38 g, 83.03 mmol) and diluted with CH_2Cl_2 (30 mL). The reaction mixture was washed with water (10 mL), brine (10mL), dried (Na_2SO_4) 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:** $[\alpha]_D$ -21.5 (*c* 0.45, $CHCl_3$); IR (neat): 3480, 2926, 2854, 1721, 1654, 1513, 1460, 1252, 938 cm^{-1}; ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $(M + NH_4)^+$, 579 $(2M+ Na)^+$. ***Z*-isomer:** $[\alpha]_D$ +115.3 (*c* 1.0, $CHCl_3$); IR (neat): 3033, 2932, 2889, 1725, 1664 cm^{-1}; ^1H NMR ($CDCl_3$, 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 $(M + NH_4)^+$.

(2*R*,3*R*,4*E*)-6-[1-(*tert.*-Butyl)-1,1-dimethylsilyl]oxy-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 CH_2Cl_2 (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 evaporated and purified the residue by column chromatography (Silica gel, 60-120 mesh, 10% EtOAc in pet. ether) to afford **25** (0.9 g, 82%) as a colorless liquid. $[\alpha]_D$ +3.62 (*c* 0.4, $CHCl_3$); IR (neat): 3033, 2929, 2855, 1460, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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).

((*E*,4*R*,5*R*)-5-(Benzyloxy)-6-[(4-methoxybenzyl)oxy]-4-methyl-2-hexenyloxy)(*tert.*-buyl)-dimethylsilane (26). To a cooled (0 °C) solution of **25** (0.5 g, 1.31 mmol) in dry THF (5 mL), NaH (0.19 g, 7.89 mmol) was added, stirred for 30 min and treated with benzyl bromide (0.27 g, 1.57 mmol) at room temperature for 6 h. The reaction mixture was quenched with sat. NH_4Cl 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 (Na_2SO_4), evaporated under reduced pressure and purified the residue by column chromatography (Silica gel, 60-120 mesh, 5% EtOAc in pet. ether) to furnish **26** (0.50 g, 82%) as a yellow liquid. $[\alpha]_D$ -21.1 (*c* 0.4, $CHCl_3$); IR (neat): 2985, 2929, 2863, 1613, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 7.27-7.26 (m, 5H) 7.19 (d, *J* 8.3 Hz, 2H), 6.8 (d, *J* 8.3 Hz, 2H), 5.5-5.45 (dd, *J* 8.7, 15.6 Hz, 1H), 5.5-5.45 (m, 1H), 4.68 (d, *J* 11.07 Hz, 1H), 4.50 (d, *J* 11.7 Hz, 1H), 4.40 (s, 2H), 4.07 (d, *J* 4.87 Hz, 2H), 3.78 (s, 3H), 3.55-3.43 (m, 3H), 2.48-2.43 (m, 1H), 1.02 (d, *J* 6.8 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm): 129.2, 128.1, 127.7, 127.6, 113.7, 81.9, 72.9, 71.2, 64.0, 55.2, 38.6, 25.9,16.4, -5.07; ESIMS: 493 $(M+ Na)^+$, 488 $(M + NH_4)^+$.

(2*R*,3*R*,4*E*)-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_2Cl_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_2Cl_2 (10 mL). The filtrate was washed with water (3 mL), brine (3 mL), dried (Na_2SO_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. $[\alpha]_D$ +13.2 (*c* 0.15, $CHCl_3$); IR (neat): 3442, 2922, 2853, 1630, 1126, 835 cm^{-1}; ^1H 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 $(M+Na)^+$.

(4*R*)-4-((1*R*,2*E*)-4-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-1-methyl-2-butenyl)-2,2-dimethyl-1,3- dioxolane (28). A solution of **27** (0.06 g, 0.002 mmol) in CH_2Cl_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. $[\alpha]_D$ +18.5 (*c* 0.2, $CHCl_3$); IR (neat): 3067, 2931, 2857, 1456 cm^{-1}; ^1H 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*,4*R*,5*R*)-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_2SO_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. $[\alpha]_D$ +11.2 (*c* 0.4, $CHCl_3$); IR (neat): 3444, 3065, 2927, 1661, 1452 cm^{-1}; ^1H 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*,4*R*,5*R*)-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_3P (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. $[\alpha]_D$ +24.3 (*c* 0.33, $CHCl_3$); IR (neat): 3063, 2928, 2864, 1606, 1451 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.31-7.26 (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 $(M + NH_4)^+$.

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