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Graphical Abstract

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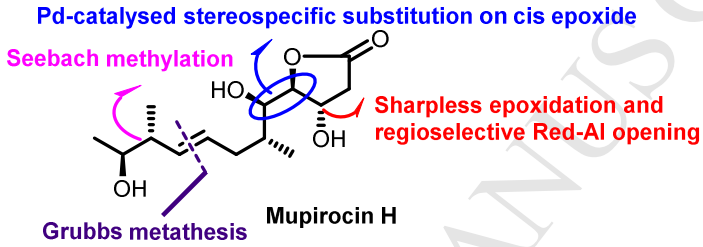
Sandip Sengupta[a], Hak Joong Kim[b], Kyung Seon Cho[a], Woon Young Song[b], and Taebo Sim*[,a,c]

[a]*Chemical Kinomics Research Center, Korea Institute of Science and Technology, Hwarangro 14-gil 5, Seongbuk-gu, Seoul 02792, Republic of Korea*
[b]*Department of Chemistry, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea*
[c]*KU-KIST Graduate School of Converging Science and Technology, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea*
Phone: +82(2)9586437; Fax: +82(2)9585189;
E-mail: tbsim@kist.re.kr



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[c]*KU-KIST Graduate School of Converging Science and Technology, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea*
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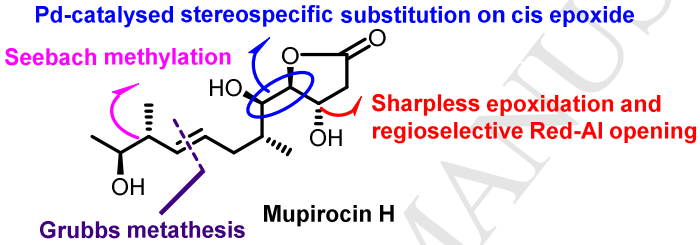

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[a]*Chemical Kinomics Research Center, Korea Institute of Science and Technology, Hwarangro 14-gil 5, Seongbuk-gu, Seoul 02792, Republic of Korea*
[b]*Department of Chemistry, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea*
[c]*KU-KIST Graduate School of Converging Science and Technology, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea*
Phone: +82(2)9586437; Fax: +82(2)9585189;
E-mail: tbsim@kist.re.kr

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ABSTRACT

A highly diastereoselective and efficient convergent synthesis of mupirocin H starting from (+)-(*R*)-Roche ester was achieved. Grubbs cross metathesis was employed as the key step in the pathway to generate an important *E*-olefin intermediate. Other processes utilized in the route include a Pd-catalysed stereoselective substitution reaction of a *cis* epoxide, Sharpless epoxidation followed by Red-Al promoted epoxide ring opening, and Seebach methylation and a TEMPO/BAIB mediated oxidation-lactonization sequence. Finally, we observed that mupirocin H inhibits SbnE, a synthetase required for staphyloferrin B biosynthesis.

1. Introduction

The closely related polyketide-derived antibiotics, collectively known as mupirocin are produced by the bacterium *Pseudomonas fluorescens* (a soil isolate, NCIB 10586). These substances are highly effective in the treatment of skin infections and are successful topical antibiotics for treatment of nasal *Staphylococcus aureus* including methicillin-resistant *S. aureus* (MRSA).[1] Mupirocin is a mixture of pseudomonic acids A-D with its main constituents being pseudomonic acid A (90%) (Figure 1).[2] These polyketides are one of the first members of this family of metabolites produced by the "AT-less" polyketide synthases (PKSs) that have their biosynthetic gene cluster sequenced.[3] Mupirocin H is derived by mutagenesis of the HMG-CoA synthase (HCS) encoding gene in *pseudomonas fluorescens*, which perturbs the normal mupirocin biosynthetic pathway (Figure 1).[4a] Studies carried out by Simpson *et al*. uncovered two new pseudomonic acid analogues named mupirocin W[4b] and mupirocin H.[4a] Mupirocin W was shown to possess a similar bioactivity to those of pseudomonic acids whereas the biological activity of mupirocin H has yet to be investigated.

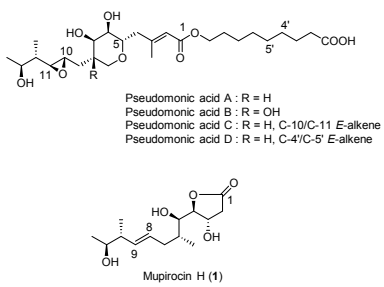


Figure 1. Structure of Pseudomonic acids and Mupirocin H (**1**)

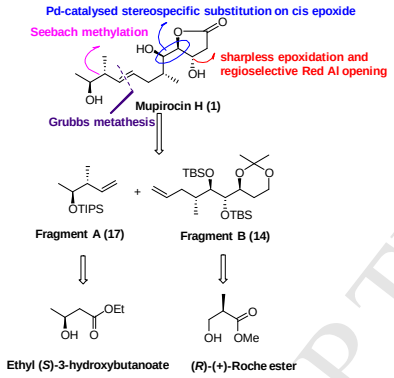
All members of the pseudomonic acid family possess similar C1-C14 terahydropyran containing frameworks with the exception for mupirocin H which contains a unique γ-lactone ring system. The structure of mupirocin H was determined first by analysis of its spectroscopic data and confirmed more recently by using total synthesis.[5a] Several groups have given attention to this substance owing to its fascinating truncated pseudomonic acid structure and the important biological activities of members of the pseudomonic acid family. Thus far, five total syntheses[5] of mupirocin H have been reported including the one described by our group in 2014.[5f] In 2011, the first total synthesis of mupirocin H was reported by Chakraborty *et al*[5a] which utilized D-glucose as a chiral pool starting material and Still-Barrish hydroboration and a Julia-Kocienski olefination processes as key steps. Willis *et al* divulged in 2012[5b] a convergent total synthesis of mupirocin H that uses a δ- to γ-lactone conversion strategy. A scalable route for the synthesis of mupirocin H, involving seven steps (longest linear sequence) and employing Suzuki–Miyaura coupling and Mukaiyama aldol reactions as key steps, was reported by She *et al*. in 2014.[5e] In that same year, an expedient total synthesis of mupirocin H that relies on the use of readily available D-ribose and a Julia–Kocienski olefination process was developed by Srihari *et al*.[5g] Finally, we reported[5f] a concise synthesis of

∗ Corresponding author. Tel.: +82(2)9586437; fax: +82(2)9585189; e-mail: tbsim@kist.re.kr

mupirocin H that employs a Grubbs cross metathesis and cobalt-mediated Reformatsky reactions as key processes. Unfortunately, the latter process lacked stereocontrol (*dr* = 9:1) and, consequently, led to a significant loss of yield at the final stage caused by a problematic diastereomer separation.

2. Results and discussion

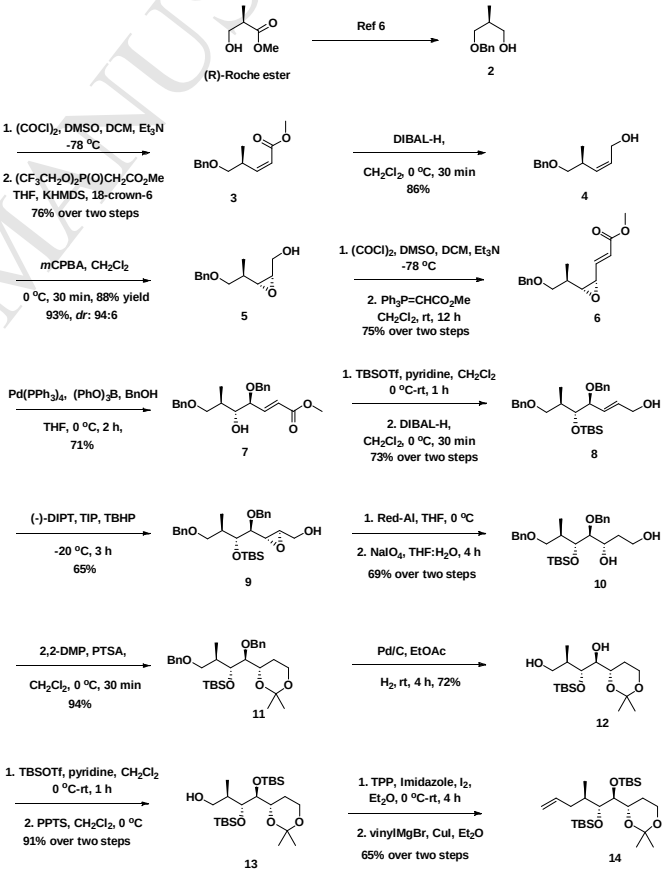
In the study described below, we devised a stereocontrolled synthesis of mupirocin H. The key steps in the pathway, involving a Pd-catalysed stereoselective substitution on *cis* epoxide and Sharpless epoxidation, generate in a fully diatereoselective manner an intermediate that undergoes Grubbs cross metathesis reaction to produce a much more advanced intermediate than the one involved in our previous preparative route. As part of our ongoing program focusing on natural products that have unique biological activities, we redesigned our previous synthesis of mupirocin H with the aim of making the route more stereoselective and efficient. The sequence developed in the current study, which begins with the commercially available (+)-(*R*)-Roche ester, is outlined in a retrosynthetic format in Scheme 1. The key steps in the sequence involve a stereoselective Pd-catalysed substitution reaction of a *cis*-epoxide, a Sharpless epoxidation followed by Red-Al epoxide opening, and Seebach methylation and Grubbs cross metathesis reactions. Owing to the fact that the Grubbs cross metathesis process produces a highly advanced intermediate, the new route for preparation of mupirocin H is not only more highly diastereoselective but it is also more efficient than the one we developed earlier.



Scheme 1

The synthesis of the important intermediate Fragment **B** (**14**, Scheme 1) in the new preparative pathway, began with conversion of commercially available (+)-(*R*)-Roche ester to the monoprotected diol **2** by using benzyl protection of the alcohol followed by ester reduction (77%, 2 steps) (Scheme 2).[6] Swern oxidation[7] of the primary alcohol **2** followed by Still-Gennari olefination[8] of the resulting aldehyde generated *cis*-*α*,*β*-unsaturated ester **3** (76%, 2 steps, *cis*/*trans* = 95/5). Chemoselective reduction of **3** using DIBAL-H[9] furnished the corresponding allylic alcohol **4** (86%), upon which perbenzoic acid epoxidation[10] produced the diastereomeric epoxy alcohols **5** (93%, *dr* = 94:6 by NMR). Separation by using column chromatography gave diastereomerically pure **5**, which was subjected to sequential Swern oxidation[7] and Wittig olefination to produce *α*,*β*-unsaturated epoxy ester **6** (75%, 2 steps).[11]

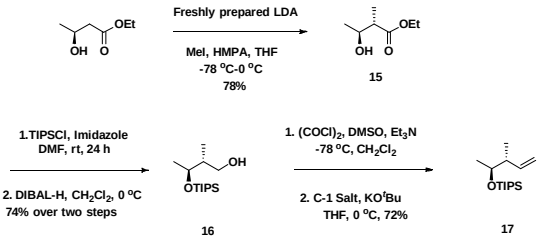
The stage was now set for conducting stereospecific nucleophilic opening of the epoxide ring in **6**.[12] Benzyl alcohol was selected as the nucleophile for this Pd-catalyzed process which generated *α*,*β*-unsaturated ester **7** in 71% yield. The configuration of the product **7** was determined unambiguously based on the ^{1}H NMR and NOSEY spectroscopic analyses of the *δ*-lactone **7'**.[13] The secondary alcohol moiety in **7** was subjected to TBS protection and ester group was then chemoselectively reduced using DIBAL-H to form allylic alcohol **8** (73%, 2 steps). Sharpless asymmetric epoxidation[14] was performed on **8** to produce the required epoxide **9** (65%). It should be noted that SAE reaction on the substance not containing a homoallylic alcohol TBS protecting group takes place in a non-diastereoselective manner presumably because of the opposite stereochemical directing effects of the allylic and homoallylic hydroxyls. 1,3-Diol **10** was then generated from epoxide **9** by reaction with Red-Al[15] followed by periodate cleavage (69%, 2 steps). The triol **10'**, TBS-deprotected compound of **10**, was converted to compound **B** for determining the stereochemistry of SAE reaction.[16] Acetonide protection of **10** formed **11** (94%), which was subjected to global benzyl removal using Pd/C to produce 1,3-diol **12** (72%). Primary alcohol **13** was then formed by sequential bis-silyl protection using TBSOTf and mono silyl-removal by using PPTS[17] (91%, 2 steps). Treatment of **13** with TPP/Iodine produced the corresponding iodide, which was directly reacted with vinyl Grignard reaction[18] to produce the required fragment **B** (**14**) (65%, 2 steps).



Scheme 2

Although the pathway for preparation of Fragment **A** used in our previous[5f] synthesis of mupirocin H was short and stereoselective, it required handling volatile substances like *trans*-2-butene and acetaldehyde, as well as the Brown crotylboration product. Consequently, a more convenient method was employed to prepare this sub-target. Specifically, Fragment **A** was synthesized starting with ethyl (*S*)-3- hydroxybutanoate in 4 steps using the route displayed in Scheme 3. Fra'ter-Seebach methylation[19] of this (*S*)-ester, accomplished using freshly prepared LDA in THF-HMPA, yielded **15** (78%, *dr* 9:1) which

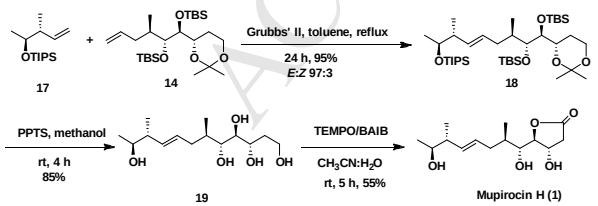
was first hydroxyl-protected with TIPS and then subjected to ester reduction using DIBAL-H[9] to form mono-alcohol **16** (74%, 2 steps). Swern oxidation of the primary alcohol moiety in **16** gave an aldehyde that underwent Wittig methylenation[20] promoted by KO^{t}Bu to generate Fragment **A** (**17**) (72%, 2 steps).



Scheme 3

A Grubbs cross metathesis (CM) process was utilized to join Fragment **A** (**17**) and Fragment **B** (**14**) (Scheme 4). The results of earlier studies of CM[21] reactions and experience gained in our previous synthesis of mupirocin H clearly demonstrated that the Grubbs' 2nd generation catalyst would be appropriate for this reaction. In addition, screening of temperature, solvent, reaction time and reactant quantities led to the identification of ideal conditions for this reaction. Importantly, owing to its volatility, Fragment **A** (**17**) was utilized in a seven-fold excess over Fragment **B** (**14**). Under the ideal conditions, CM reaction between **14** and **17** took place efficiently to form **18 (**95%, *E*:*Z* = 97:3**)** by using Grubbs' II catalyst in refluxing toluene for 24 h at 110 °C. Pure *E*-**18** was then subjected to global deprotection by using PPTS[17,22] in methanol to form pentaol **19** (85%). Oxidation followed by lactonization was then effectively carried out in one step by treating **19** with TEMPO/BAIB.[23] This sequence produced mupirocin H (**1**) in 55% yield. The analytical data (^{1}H NMR, ^{13}C NMR, IR, HRMS and optical rotation) collected for synthetic **1** match those reported for the isolated natural product as well as those for the substance prepared in our earlier study.[4,5]

In the initial phase of biological studies, we observed that mupirocin H inhibits (43.7% inhibition at 100 uM) SbnE, a synthetase required for the biosynthesis of staphyloferrin, a carboxylate-type siderophore required for iron uptake.[24] Therefore, mupirocin H has the potential of being a novel starting point for identifying unique antibiotics that target SbnE. In this context, the synthetic strategy devised in this effort should be readily adaptable to the design of routes to prepare derivatives of mupirocin H that are needed to carry out biological studies aimed at testing this proposal.



Scheme 4

In conclusion, the current effort led to the development of a convergent pathway for the diastereoselective and efficient synthesis of mupirocin H (17 steps in its longest linear sequence, 21 steps overall, and 2.5% overall yield from commercial sources). The route relies on the use of a Still-Gennari olefination, Pd-catalysed stereoselective *cis* epoxide substitution reaction, Sharpless epoxidation followed by Red-Al epoxide ring opening and Fra'ter-Seebach methylation to generate two key fragments that contain correct absolute configurations at all six of the stereogenic centers in the target. Grubbs cross metathesis was then utilized as a key coupling reaction joining the two fragments and generating the desired *E*-olefin stereochemistry. Finally, a TEMPO/BAIB mediated oxidation-lactonization sequence was utilized to complete the synthesis of mupirocin H.

3. Experimental Section

3.1. General Experimental Methods

All reactions were carried out under inert atmosphere of argon or nitrogen using standard syringe, septa, and cannula techniques unless otherwise mentioned. Reactions were monitored by using TLC with 0.25 mm E. Merck precoated silica gel plates (60 F_{254}). Reaction progress was monitored by using TLC with a UV lamp, ninhydrin, or *p*-anisaldehyde stain for detection purposes. Commercially available reagents were used without further purification. All solvents were purified by using standard techniques. Purification of products was carried out by using silica gel column chromatography using Kieselgel 60 Art. 9385 (230–400 mesh). The purity of all compounds was determined to be over 95% by using a Waters LCMS system (Waters 2998 Photodiode Array Detector, Waters 3100 Mass Detector, Waters SFO System Fluidics Organizer, Water 2545 Binary Gradient Module, Waters Reagent Manager, Waters 2767 Sample Manager) using SunFireTM C18 column (4.6 × 50 mm, 5 µm particle size): solvent gradient = 60% (or 95%) A at 0 min, 1% A at 5 min. Solvent A = 0.035% TFA in H_2O; Solvent B = 0.035% TFA in MeOH; flow rate : 3.0 (or 2.5) mL/min. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker 400 MHz FT-NMR (400 MHz for ^{1}H, and 100 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to $CHCl_3$ (δ = 7.26) for ^{1}H NMR and $CHCl_3$ (δ = 77.0) for ^{13}C NMR. Standard abbreviations are used for denoting the signal multiplicities. Infrared spectra were measured on FT-IR Nicolet iS10 spectrometer. Samples were recorded under neat or as KBr optics. High-resolution mass spectra (HRMS) were recorded on a QTOF mass spectrometer. Optical rotations were measured on a Rudolph Autopol III polarimeter at the wavelength of sodium D-line (589 nm) at room temperature.

*3.1.1. Methyl(S,Z)-5-(benzyloxy)-4-methylpent-2-enoate **(3)*:**

To a solution of oxalyl chloride (7.3 mL, 8.37 mmol) in CH_2Cl_2 (100 mL) was added DMSO (7 mL, 99 mmol) at -78 °C. After stirring for 10 min at -78 °C, a solution of primary alcohol **2** (10.0 g, 55.5 mmol) in CH_2Cl_2 (100 mL) was added dropwise to the mixture. The solution was stirred for 15 min at the same temperature and then Et_3N (47.2 mL, 332 mmol) was added dropwise. The mixture was stirred at that same temperature for 45 min and then poured into the saturated NH_4Cl solution (60 mL). The organic layer was separated and washed with saturated $NaHCO_3$ solution (50 mL), dried over $MgSO_4$ and concentrated under reduce pressure to give the crude aldehyde, which was used in the next step without purification.

A solution of phosphonate (17.5 g, 55 mmol), 18-crown-6 (26.5 gm, 100 mmol) in anhydrous THF (200 mL) was cooled to -78 °C and treated with 1 M KHMDS (55 mL, 55 mmol) solutionfor 30 min. A solution of aldehyde (50 mmol) in THF was added slowly and the resulting mixture was stirred for 1 h at -78 °C. The reaction was quenched with saturated NH_4Cl solution (60 mL) and extracted with ether (3 × 50 mL). The combined ether extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford compound **3** (9.7 g,

76% over two steps) as a yellow oil. R_f = 0.2 (10% EtOAc/hexane); $[\alpha]^{25}_D$ +56.2 (*c* 2.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 6.14 (dd, *J* = 11.5, 9.8 Hz, 1H), 5.81 (dd, *J* = 11.5, 1.0 Hz, 1H), 4.52 (d, *J* = 1.8 Hz, 2H), 3.90-3.83 (m, 1H), 3.71 (s, 3H), 3.40 (dd, *J* = 5.7, 1.5 Hz, 2H), 1.08 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 153.0, 138.5, 128.3, 127.5, 127.4, 119.3, 74.5, 72.7, 51.0, 33.2, 16.8.

*3.1.2. (S,Z)-5-(Benzyloxy)-4-methylpent-2-en-1-ol (**4**)*

To a solution of **3** (7 g, 29.9 mmol) in anhydrous CH_2Cl_2 (100 mL), DIBAL-H (53.7 mL, 75 mmol, 20% solution in toluene) was added slowly for 15 min at 0 °C. The mixture was stirred for 1 h at 0 °C before being quenched with methanol (10 mL) and aqueous saturated sodium potassium tartarate solution (50 mL). The mixture was passed through a small pad of celite and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and subjected to silica gel column chromatography to furnish *cis* allylic alcohol **4** (5.31 g, 86%) as a colorless liquid. R_f = 0.4 (30% EtOAc/hexane); $[\alpha]^{26}_D$ -1.2 (*c* 0.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 5.83-5.77 (m, 1H), 5.35 (t, *J* = 10.7 Hz, 1H), 4.51 (s, 2H), 4.20 (dd, *J* = 12.1, 7.9 Hz, 1H), 3.99-3.93 (m, 1H), 3.38 (dd, *J* = 8.8, 5.0 Hz, 1H), 3.17 (t, *J* = 8.9 Hz, 1H), 2.94-2.83 (m, 1H), 2.39-2.38 (brs, 1H), 0.96 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 136.6, 129.4, 128.4, 128.3, 127.7, 127.5, 74.7, 73.3, 58.0, 32.5, 17.3.

*3.1.3. ((2S,3R)-3-((R)-1-(Benzyloxy)propan-2-yl)oxiran-2-yl)methanol (**5**)*

To a solution of **4** (5 g, 24.3 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added *m*CPBA (10.7 g, 43.68 mmol; 70%) slowly portion wise and allow to stir at that temperature for 30 min for full conversion. The reaction was quenched with saturated $NaHCO_3$ solution and stir for another 15 min. The mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was subjected to silica gel column chromatography to afford compound **5** (5.01 g, 93%) as major isomer. R_f = 0.3 (30% EtOAc/hexane); $[\alpha]^{25}_D$ +8.5 (*c* 4.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 4.55 (d, *J* = 0.9 Hz, 2H), 3.89(dd, *J* = 12.1, 4.0 Hz, 1H), 3.68 (dd, *J* = 12.1, 6.9 Hz, 1H), 3.57 (dd, *J* = 9.0, 4.9 Hz, 1H), 3.51 (dd, *J* = 9.0, 6.1 Hz, 1H), 3.18 (dt, *J* = 6.9, 4.1 Hz, 1H), 2.93 (dd, *J* = 9.4, 4.4 Hz, 1H), 1.76-1.66 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 128.4, 128.3, 127.5, 73.3, 73.2, 60.8, 59.3, 56.2, 33.5, 13.9.

*3.1.4 Methyl(E)-3-((2S,3R)-3-((R)-1-(benzyloxy)propan-2-yl)oxiran-2-yl)acrylate (**6**)*

To a solution of oxalyl chloride (2.89 mL, 33.8 mmol) in CH_2Cl_2 (50 mL) was added DMSO (2.56 mL, 36 mmol) at -78 °C. After 10 min at -78 °C, a solution of primary alcohol **5** (5.0 g, 22.5 mmol) in CH_2Cl_2 (50 mL) was added dropwise to the reaction mixture. The solution was stirred for 30 min at the same temperature and then Et_3N (18.8 mL, 135.6 mmol) was added dropwise. The mixture was stirred at that same temperature for 45 min and then poured into the saturated NH_4Cl solution (50 mL). The organic layer was washed with saturated $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to get the crude aldehyde, which without purification was used in the next reaction.

A solution of crude aldehyde in CH_2Cl_2 was treated with C-2 Wittig ylide (11.7 g, 33.7 mmol) and then stirred for 6 h at room temperature. The organic layer was washed with H_2O (30 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford compound **6** (4.6 g, 75% over two steps) as a yellow oil. R_f = 0.2 (10% EtOAc/hexane); $[\alpha]^{27}_D$ +41.0 (*c* 0.73, $CHCl_3$); IR (KBr): 2964, 2859, 1721, 1656, 1454, 1275, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.27 (m, 5H), 6.83 (dd, *J* = 15.6, 6.5 Hz, 1H), 6.15 (dd, *J* = 15.6, 0.8 Hz, 1H), 4.55 (d, *J* = 1.8 Hz, 2H), 3.75 (s, 3H), 3.60-3.50 (m, 3H), 3.11(dd, *J* = 9.4, 4.4 Hz, 1H), 1.71-1.61 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 141.9, 138.4, 128.3, 127.5, 127.5, 124.9, 73.2, 72.9, 61.6, 54.5, 51.7, 33.1, 13.6. HRMS (ESI): calcd. for $C_{16}H_{20}O_4Na$ $[M + Na]^+$ 299.1362; found 299.1361.

*3.1.5. Methyl(4S,5R,6R,E)-4,7-bis(benzyloxy)-5-hydroxy-6-methylhept-2-enoate (**7**)*

To a solution of *α,β*-unsaturated *γ,δ*-epoxy ester **6** (4 g, 14.5 mmol) in THF (40 mL) was added triphenyl borate (6.3 g, 21.7 mmol), benzyl alcohol (6.78 mL, 65.2 mmol), and $Pd(PPh_3)_4$ (1.6 g, 10 mol%) at 0 °C and the resulting mixture was stirred at 0 °C for 10 min and then 4 h at room temperature, and passed through a pad of celite. The filtrate was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **7** (3.95 g, 71%) as a colorless liquid. R_f = 0.2 (30% EtOAc/hexane); $[\alpha]^{27}_D$ +20.5(*c* 1.23, $CHCl_3$); IR (KBr): 3455, 2068, 1644, 1454, 1072, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (m, 10H), 7.01 (dd, *J* = 15.9, 6.8 Hz, 1H), 6.08 (dd, *J* = 15.9, 1.1 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.45 (d, *J* = 5.4 Hz, 2H), 4.33 (d, *J* = 11.6 Hz, 1H), 3.98-3.95 (m, 1H), 3.76 (s, 3H), 3.72-3.67 (m, 1H), 3.56 (dd, *J* = 9.2, 4.5 Hz, 1H), 3.48 (dd, *J* = 9.0, 4.4 Hz, 1H), 3.22 (d, *J* = 5.0 Hz, 1H), 2.01-1.92 (m, 1H), 1.00 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 145.0, 137.9, 137.6, 128.5, 128.4, 127.9, 127.8, 127.7, 127.7, 123.3, 79.7, 76.5, 73.4, 73.1, 71.2, 51.6, 34.6, 14.5; HRMS (ESI): calcd. for $C_{23}H_{28}O_5Na$ $[M + Na]^+$ 407.1956; found 407.1986.

*3.1.6. (4S,5R,6R,E)-4,7-bis(Benzyloxy)-5-((tert-butyldimethylsilyl)oxy)-6-methylhept-2-en-1-ol (**8**)*

To a solution of **7** (3.6 g, 9.37 mmol) in anhydrous CH_2Cl_2 (30 mL), was added 2,6-lutidine (4.3 mL, 37.5 mmol) followed by TBSOTf (3.4 mL, 18.7 mmol) slowly at 0 °C. The mixture was stirred for 1 h at 0 °C and quenched with water (3 mL) and washed with saturated $NaHCO_3$ solution (10 mL). Organic layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure to give crude product, which was used for the next step.

To a solution of crude product in anhydrous CH_2Cl_2 (30 mL) was added DIBAL-H (16.7 mL, 23.4 mmol, 20% solution in toluene) slowly for 15 min at 0 °C. The mixture was stirred for 1 h at 0 °C and quenched with methanol (3 mL) and saturated sodium potassium tartarate solution (10 mL). The mixture was passed through a small pad of celite and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure to give a residue that was subjected to silica gel column chromatography to furnish the allylic alcohol **8** (3.21 g, 73% over two steps) as a colorless liquid. R_f = 0.6 (10% EtOAc/hexane); $[\alpha]^{24}_D$ +7.4 (*c* 0.46, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.26 (m, 10H), 5.81 (dt, *J* = 15.7, 5.3 Hz, 1H), 5.68 (ddt, *J* = 15.7, 8.0, 1.4 Hz, 1H), 4.53-4.29 (m, 4H), 4.17 (d, *J* = 5.1 Hz, 2H), 3.82 (dd, *J* = 7.9, 4.6 Hz, 1H), 3.73 (dd, *J* = 5.6, 4.7 Hz, 1H), 3.59 (q, *J* = 4.5 Hz, 1H),

3.34 (dd, *J* = 9.0, 7.4 Hz, 1H), 2.04-1.95 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.85 (s, 9H), 0.03 (d, *J* = 3.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 138.5, 133.7, 129.2, 128.2, 128.2, 127.8, 127.5, 127.4, 81.05, 77.2, 76.5, 72.9, 72.6, 70.2, 63.2, 37.3, 26.1, 18.3, 14.5, -3.7, -4.6; HRMS (ESI): calcd. for $C_{28}H_{42}O_4SiNa$ $[M + Na]^+$ 493.2750; found 493.2749.

*3.1.7. ((2R,3S)-3-((1S,2R,3R)-1,4-bis(Benzyloxy)-2-(tert-butyldimethylsilyloxy)-3-methylbutyl)oxiran-2-yl)methanol (**9**)*

To a solution of (-)-DIPT (0.5 mL, 2.63 mmol) in dry CH_2Cl_2 (20 mL) containing 4Å MS (1 g) were sequentially added $Ti(O^iPr)_4$ (0.78 mL, 2.63 mmol) and 5 M TBHP in toluene (5.27 mL, 26.36 mmol) at -30 ^{o}C. The mixture was stirred for 30 min and treated with a solution of alcohol **8** (3.1 g, 6.59 mmol) in CH_2Cl_2 (10 mL) and stirred for an additional 12 h at -30 ^{o}C. The mixture was quenched with 15 mL water and 30% aqueous NaOH solution, and diluted with saturated with brine (5 mL) and stirred vigorously for 30 min at room temperature. The mixture was filtered through a pad of celite and the filter cake was washed with CH_2Cl_2 (20 mL). The filtrate was washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **9** (2.1 g, 65%) as a viscous liquid. R_f = 0.3 (20% EtOAc/hexane); $[\alpha]^{25}_D$ +3.2 (*c* 2.82, $CHCl_3$); IR (KBr): 3451, 2955, 2929, 2856, 1636, 1455, 1252, 1093 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.26 (m, 10H), 4.55 (s, 2H), 4.44(q, *J* = 12.1 Hz, 2H), 3.88 (d, *J* = 12.9 Hz, 1H), 3.85 (q, *J* = 3.4 Hz, 1H), 3.59-3.53 (m, 3H), 3.39 (dd, *J* = 9.0, 6.7 Hz, 1H), 3.24-3.20 (m, 1H), 3.18-3.14 (m, 1H), 2.14-2.05 (m, 1H), 0.99(d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 138.3, 128.3, 128.2, 127.7, 127.6, 127.5, 127.4, 78.5, 75.4, 73.0, 72.9, 72.4, 61.4, 55.8, 54.8, 37.4, 26.0, 18.3, 14.4, -4.0, -4.8; HRMS (ESI): calcd. for $C_{28}H_{42}O_4SiNa$ $[M + Na]^+$ 509.2699; found 509.2701.

*3.1.8. (3S,4S,5R,6R)-4,7-bis(Benzyloxy)-5-(tert-butyldimethylsilyloxy)-6-methylheptane-1,3-diol (**10**)*

To a solution of epoxy alcohol **9** (2.0 g, 4.11 mmol) in THF (20 mL) was added Red-Al (1.46 g, 5.59 mmoL) and the resulting mixture was stirred for 4 h at 0 ^{o}C. The mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and diluted with EtOAc (30 mL). The organic layer was extracted with EtOAc (3 × 30 mL) and the combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure to afford the crude 1,3-diol as a colorless liquid which contained a small amount of the 1,2-diol. To a solution of the crude diol in THF:H_2O (2:1) (15 mL) was added sodium meta-periodate at 0 ^{o}C and the mixture was stirred for 4 h at room temperature. The mixture was filtered through a pad of celite and the organic layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **10** (1.38 g, 69% over two steps) as a colourless liquid. R_f = 0.8 (10% EtOAc/hexane); $[\alpha]^{25}_D$ -14.4 (*c* 1.9, $CHCl_3$); IR (KBr): 3442, 2955, 2856, 1636, 1454, 1069, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 10H), 4.69-4.62 (m, 1H), 4.48-4.40 (m, 3H), 4.05-3.97 (m, 1H), 3.93 (dd, *J* = 6.7, 2.6 Hz, 1H), 3.83-3.77 (m, 2H), 3.58 (dd, *J* = 9.2, 5.1 Hz, 1H), 3.42-3.34 (m, 2H), 2.17-2.11 (m, 1H), 1.97-1.89 (m, 1H), 1.78-1.69 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.08 (d, *J* = 17.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 138.1, 128.2, 128.2, 127.7, 127.5, 127.4, 83.7, 75.8, 73.1, 72.9, 72.3, 61.8, 37.8, 34.6, 25.9, 18.1, 14.8, -4.0, -4.9; HRMS (ESI): calcd. for $C_{28}H_{44}O_5SiNa$ $[M + Na]^+$ 511.2856; found 511.2854.

*3.1.9. ((1S,2R,3R)-1,4-bis(Benzyloxy)-1-((S)-2,2-dimethyl-1,3-dioxan-4-yl)-3-methylbutan-2-yloxy)(tert-butyl)dimethylsilane (**11**)*

To a solution of **10** (1.2 g, 2.45 mmol) in CH_2Cl_2 (10 mL) was added 2,2-dimethoxy propane (1.3 mL, 10 mmol) followed by PTSA (cat.) at 0 ^{o}C. The mixture was warmed to room temperature and stirred for 30 min and quenched with water (10 mL). The organic layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford **11** (1.2 g, 94%) as a colourless liquid. R_f = 0.4 (5% EtOAc/hexane); $[\alpha]^{26}_D$ -10.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.26 (m, 10H), 4.74-4.63 (m, 2H), 4.42 (s, 2H), 4.19-4.15 (m, 1H), 3.95 (td, *J* = 12.2, 2.8 Hz, 1H), 3.86 (dd, *J* = 11.7, 4.0 Hz, 1H), 3.77 (t, *J* = 4.9 Hz, 1H), 3.63 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.49 (t, *J* = 4.9 Hz, 1H), 3.32 (dd, *J* = 8.9, 8.0 Hz, 1H), 2.18-2.10 (m, 1H), 1.87-1.75 (m, 1H), 1.55-1.51 (m, 1H), 1.39 (d, *J* = 17.0 Hz, 6H), 1.10(d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.04 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 138.7, 128.4, 128.3, 128.2, 128.0, 127.8, 127.6, 127.4, 127.3, 98.2, 83.5, 73.9, 73.7, 73.0, 72.9, 69.5, 60.0, 37.4, 30.0, 26.0, 19.0, 18.2, 14.6, -4.0, -4.6.

*3.1.10. (1S,2R,3R)-2-(tert-Butyldimethylsilyloxy)-1-((S)-2,2-dimethyl-1,3-dioxan-4-yl)-3-methylbutane-1,4-diol (**12**)*

To a solution of **11** (1 g, 1.89 mmol) in EtOAc (10 mL) under H_2 was added Pd/C (10 mol%) and stirred for 4 h at room temperature. The mixture was filtered through a pad of celite, washed with EtOAc and concentrated in vacuum. The residue was subjected to silica gel column chromatography to afford compound **12** (473 mg, 72%) as a white solid. R_f = 0.3 (30% EtOAc/hexane); $[\alpha]^{26}_D$ -20.6 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12-4.04 (m, 1H), 3.99-3.92 (m, 1H), (m, 2H), 3.66 (dd, *J* = 11.4, 8.4 Hz, 1H), 3.59 (t, *J* = 6.6 Hz, 1H), 3.43(dd, *J* = 11.4, 3.4 Hz, 1H), 3.35 (brs, 2H), 2.05-1.95 (m, 1H), 1.79-1.69 (m, 1H), 1.64-1.59 (m, 1H), 1.44 (s, 3H), 1.36 (s, 3H), 0.92 (d, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.09 (d, *J* = 1.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 98.1, 77.3, 76.9, 76.6, 75.5, 74.5, 68.9, 63.4, 59.5, 37.5, 29.7, 26.8, 25.8, 19.2, 18.1, 14.5, -4.4, -4.5; HRMS (ESI): calcd. for $C_{17}H_{36}O_5SiNa$ $[M + Na]^+$ 371.2230; found 371.2240.

*3.1.11. (2R,3R,4S)-3,4-bis(tert-Butyldimethylsilyloxy)-4-((S)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methylbutan-1-ol (**13**)*

To a solution of **12** (400 mg, 1.15 mmol) in anhydrous CH_2Cl_2 (5 mL) was added 2,6 lutidine (1.06 mL, 9.2 mmol) followed by TBSOTf (0.83 mL, 4.6 mmol) slowly (dropwise) at 0 ^{o}C. The mixture was stirred for 1 h at 0 ^{o}C and quenched with water (2 mL) and saturated $NaHCO_3$ solution (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure to give crude product, which was used for the next step without purification.

To a solution of crude tris-TBS compound in CH_2Cl_2 (5 mL) was added PPTS (cat.) at 0 ^{o}C and the resulting mixture was stirred for 4-5 h, quenched with water (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to get compound **13** (483 mg, 91% over two steps) as a colorless oil. R_f = 0.3 (20% EtOAc/hexane); $[\alpha]^{24}_D$ +3.4 (*c* 2.4, $CHCl_3$); IR (KBr): 3443, 2957,

2930, 2885, 2857, 1636, 1472, 1253, 1099, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.98-3.91 (m, 2H), 3.89-3.84 (m, 1H), 3.80 (dd, *J* = 5.8, 2.4 Hz, 1H), 3.65-3.63 (m, 2H), 3.54 (dd, *J* = 10.8, 4.0 Hz, 1H), 2.13-2.04 (m, 1H), 1.67-1.54 (m, 2H), 1.42 (s, 3H), 1.37 (s, 3H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.93 (s, 9H), 0.90 (s, 9H), 0.15 (d, *J* = 2.2 Hz, 6H), 0.12 (d, *J* = 1.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 98.0, 79.3, 77.9, 69.4, 65.5, 59.8, 36.8, 29.6, 27.8, 26.0, 25.9, 19.1, 18.2, 18.1, 15.8, -3.5, -3.8, -4.6, -4.9; HRMS (ESI): calcd. for $C_{23}H_{50}O_5Si_2Na$ $[M + Na]^+$ 485.3095; found 485.3097.

*3.1.12. (5S,6R)-5-((S)-2,2-Dimethyl-1,3-dioxan-4-yl)-2,2,3,3,8,8,9,9-octamethyl-6-((R)-pent-4-en-2-yl)-4,7-dioxa-3,8-disiladecane (**14**)*

To a solution of alcohol **13** (400 mg, 0.86 mmol) in diethyl ether (3 mL) was added successively triphenylphosphine (270 mg, 1.03 mmol) and imidazole (87 mg, 1.29 mmol) followed by iodine (350 mg, 1.37 mmol) at 0 °C. The mixture was stirred for 6 h at 0 °C, quenched with saturated $Na_2S_2O_3$ solution (2 mL) and diluted with Et_2O (5 mL). The organic layer was extracted with Et_2O (3 × 5 mL) and the combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude iodo compound as a colorless liquid which was used for the next reaction without purification.

To a suspension of CuI (165 mg, 0.86 mmol) in ether (5 mL) was added 1 M vinyl Grignard in THF (2.6 mL) slowly at 0 °C. The mixture was stirred for 30 min and treated with the crude iodo compound in Et_2O (5 mL) slowly at 0 °C. The mixture was stirred for 5 h at same temperature and quenched with saturated NH_4Cl solution (2 mL). The mixture was diluted with EtOAc (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford **14** (263 mg, 65% over two steps) as a colorless liquid. R_f = 0.8 (5% EtOAc/hexane); $[\alpha]^{24}_D$ -37.6 (*c* 0.1, $CHCl_3$); IR (KBr): 2956, 2927, 1639, 1257, 1099, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.84-5.73 (m, 1H), 5.04-4.92 (m, 2H), 4.15-4.07 (m, 1H), 3.96 (t, *J* = 12.1 Hz, 1H), 3.80 (dd, *J* = 11.6, 5.6 Hz, 1H), 3.73-3.66 (m, 1H), 3.65-3.61 (m, 1H), 2.50-2.46 (m, 1H), 1.99-1.90 (m, 1H), 1.88-1.75(m, 1H), 1.74-1.63 (m, 1H), 1.57-1.51 (m, 1H), 1.43 (s, 6H), 0.94-0.91 (m, 21H), 0.16 (d, *J* = 4.5 Hz, 6H), 0.12 (d, *J* = 3.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 115.0, 97.7, 78.2, 77.7, 69.4, 59.1, 36.5, 35.1, 25.3, 20.0, 19.8, 19.3, 17.9, -4.2, -4.2; HRMS (ESI): calcd. for $C_{25}H_{52}O_4Si_2Na$ $[M + Na]^+$ 495.3302; found 495.3302.

*3.1.13. Ethyl(2S,3S)-3-hydroxy-2-methylbutanoate (**15**)*

To a solution of diisopropylamine (10.6 mL, 75.7 mmol) in THF (100 mL) at -78 °C was added 2.5 M *n*BuLi (30.3 mL, 75.7 mmol) and warmed to 0 °C. The r mixture was cooled to -78 °C and after 30 min a solution of ethyl (*S*)-3-hydroxybutanoate (4.0 g, 30.3 mmol) in dry THF (50 mL) was added slowly. Stirring was continued for 1 h at the same temperature. To the mixture was added HMPA (8.4 mL, 48.5 mmol) followed by methyl iodide (5.66 mL, 90.9 mmol) in THF (15 mL). The mixture was stirred at -78 °C for 3 h and at 0 °C for 2 h. The mixture was quenched with saturated NH_4Cl solution (20 mL) and acidified with dilute HCl, and then extracted with EtOAc (2 × 60 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography to afford compound **15** (3.4 g, 78%) as a colorless liquid. R_f = 0.3 (30% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 4.14 (q, *J* = 7.1 Hz, 2H), 3.88-3.82 (m, 1H), 2.69 (d, *J* = 2.9 Hz, 1H), 2.45-2.37 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.96 (d, *J* = 6.3 Hz, 3H), 1.15 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 69.2, 60.4, 46.8, 20.4, 14.0, 13.7; LCMS (ESI): 147 $(M+H)^+$.

*3.1.14. (2R,3S)-2-Methyl-3-(triisopropylsilyloxy)butan-1-ol (**16**)*

To a solution of *β*-hydroxy ester **15** (3 g, 20.5 mmol) in DMF (30 mL) was added imidazole (2.09 g, 30.8 mmol) and TIPSCl (5.26 mL, 24.6 mmol) successively at 0 °C. The mixture was warmed and stirred at room temperature for 24 h. The mixture was diluted with EtOAc (50 mL) and water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was used directly for next reaction without purification.

To a solution of the crude product in anhydrous CH_2Cl_2 (50 mL) was added DIBAL-H (36.6 mL, 51.2 mmol, 20% solution in toluene) at 0 °C slowly for 15 min. The mixture was stirred for 1 h at 0 °C and quenched with methanol (5 mL) and saturated sodium potassium tartarate solution (1 mL). The mixture was passed through a small pad of celite and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to furnish alcohol **16** (3.94 g, 74% over two steps) as a colorless liquid. R_f = 0.3 (20% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 4.02-3.96 (m, 1H), 3.68 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.53 (dd, *J* = 10.9, 6.1 Hz, 1H), 2.78 (s, 1H), 1.71-1.62 (m, 1H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.05 (s, 18H), 0.94 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 72.9, 65.7, 42.2, 21.2, 18.1, 18.0, 17.6, 13.6, 12.7; LCMS (ESI): 261 $(M+H)^+$.

*3.1.15. Triisopropyl((2S,3R)-3-methylpent-4-en-2-yloxy)silane (**17**)*

To a solution of oxalyl chloride (0.98 mL, 11.5 mmol) in CH_2Cl_2 (5 mL) was added DMSO (0.9 mL, 12.3 mmol) at -78 °C and stir for 10 min. A solution of primary alcohol **16** (2 g, 7.69 mmol) in CH_2Cl_2 (25 mL) was added dropwise to the mixture, which was then stirred for 30 min at the same temperature. To the mixture was added Et_3N (6.4 mL, 46.1 mmol) dropwise and stirring was continued for 45 min. The mixture was poured into saturated NH_4Cl solution (20 mL) and then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to get the crude aldehyde, which was used in the next step without purification.

To a suspension of C-1 salt (9.4 g, 23.07 mmol) in THF (25 mL) was added KO^{t}Bu (1.7 g, 15.38 mmol) at 0 °C portion wise and the resulting mixture was stirred for 10 min. A solution of crude aldehyde in anhydrous THF (10 mL) was added slowly to the mixture and stirring was continued at the same temperature for 30 min. The mixture was quenched with water (10 mL) and diluted with EtOAc (30 mL), and then extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford **17** (1.3 g, 72% over 2 steps) as a colorless liquid. R_f = 0.8 (5% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 5.83-5.75 (m, 1H), 5.04-5.01 (m, 1H), 4.98 (d, *J* = 1.1 Hz, 1H), 3.97-3.92 (m, 1H), 2.36-2.28 (m, 1H), 1.08-1.06 (m, 21H), 1.04(d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 114.2, 71.6, 45.3, 19.3, 18.2, 18.1, 13.7, 12.6; LCMS (ESI): 257 $(M+H)^+$.

*3.1.16. (5S,6R)-5-(2,2-Dimethyl-1,3-dioxan-4-yl)-2,2,3,3,8,8,9,9-octamethyl-6-((2R,6R,7S,E)-6-methyl-7-(triisopropylsilyl)oct-4-en-2-yl)-4,7-dioxa-3,8-disiladecane (**18**)*

To a solution of **17** (380 mg, 1.48 mmol) in toluene (1 mL) under N_2 was added **14** (100 mg, 0.2 mmol) in toluene (1 mL). Grubbs' II catalyst (50 mg) was added to the mixture which was then heated at 110 ^oC for 24 h. The mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography to afford compound **18** (125 mg, 95%) as a colourless liquid. R_f = 0.8 (5% EtOAc/hexane); $[\alpha]^{24}_D$ -6.3 (*c* 1.7, $CHCl_3$); IR (KBr): 2958, 2858, 1633, 1254, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.36-5.30 (m, 2H), 4.09-4.03 (m, 1H), 3.94-3.81 (m, 2H), 3.67-3.57 (m, 2H), 3.41 (t, *J* = 5.4 Hz, 1H), 2.37-2.23 (m, 1H), 2.01-1.91 (m, 1H), 1.85-1.65 (m, 4H), 1.42 (s, 6H), 1.09-1.02 (m, 21H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.91-0.87 (m, 27H), 0.09 (d, *J* = 5.5 Hz, 6H), 0.06 (d, *J* = 4.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.2, 128.9, 98.2, 78.8, 77.9, 77.2, 69.6, 60.0, 44.2, 35.9, 30.1, 29.7, 26.2, 20.6, 19.4, 18.5, 18.2, 16.8, 14.3, -3.5, -3.9; HRMS (ESI): calcd. for $C_{25}H_{52}O_4Si_2Na$ $[M + Na]^+$ 723.5211; found 723.5204.

*3.1.17. (4S,5R,6R,10R,11S,E)-6,10-Dimethyldodec-8-ene-1,3,4,5,11-pentaol (**19**)*

To a solution of **18** (100 mg, 0.15 mmol) in methanol (2 mL) was added PPTS (200 mg) and the resulting mixture was stirred for 4 h and concentrated under reduced pressure. The residue was diluted with EtOAc (5 mL) and washed with water (2 mL) and brine solution successively, and then extracted with EtOAc (4 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford **19** (30 mg, 85%) as a sticky colorless oil. R_f = 0.2 (10% MeOH/$CHCl_3$); $[\alpha]^{27}_D$ -9.6 (*c* 0.2, $CHCl_3$); IR (KBr): 3451, 2085, 1635, 564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.40-5.24 (m, 2H), 3.82-3.77 (m, 1H), 3.71-3.59 (m, 2H), 3.55-3.47 (m, 1H), 3.43 (dd, *J* = 8.8, 5.0 Hz, 1H), 3.33 (dd, *J* = 8.8, 2.8 Hz, 1H), 2.24-2.17 (m, 1H), 2.07-2.01 (m, 1H), 1.96-1.87 (m, 1H), 1.86-1.70 (m, 2H), 1.63-1.55 (m, 1H), 0.99 (d, *J* = 6.2 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.4, 131.4, 78.3, 74.9, 72.5, 72.2, 60.3, 45.3, 36.0, 35.1, 34.2, 20.2, 17.2, 16.5; HRMS (ESI): calcd. for $C_{14}H_{28}O_5Na$ $[M + Na]^+$ 299.1834; found 299.1836.

*3.1.18. (4S,5S)-5-((1R,2R,6R,7S,E)-1,7-Dihydroxy-2,6-dimethyloct-4-enyl)-4-hydroxydihydrofuran-2(3H)-one (**1**) (Mupirocin H)*

To a solution of pentaol **19** (20 mg, 0.07 mmol) in CH_3CN:H_2O (3:2, 2 mL) was added BAIB (45 mg, 0.14 mmol) followed by catalytic TEMPO at room temperature. The mixture was stirred for 5 h at the same temperature, diluted with EtOAc (5 mL) and water (5 mL), and then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford mupirocin H (**1**) (10 mg, 55%) as a colorless oil. R_f = 0.3 (10% MeOH/$CHCl_3$); $[\alpha]^{24}_D$ +28.7 (*c* 0.5, $CHCl_3$ (lit. $[\alpha]^{24}_D$ +30.5, *c* 1.3, $CHCl_3$)); IR (KBr): 3407, 2960, 2922, 2853, 1742, 1668, 1457, 1376, 1259, 1195, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.60 (ddd, *J* = 14.9, 8.4, 6.0 Hz, 1H), 5.38 (dd, *J* = 15.4, 8.6 Hz, 1H), 4.59 (m, 1H), 4.41 (dd, *J* = 5.6, 3.4 Hz, 1H), 3.58 (dd, *J* = 6.6, 6.2 Hz, 1H), 3.51 (m, 1H), 2.93 (dd, *J* = 18.1, 7.5 Hz, 1H), 2.51 (dd, *J* = 18.1, 4.4 Hz, 1H), 2.34-2.18 (m, 2H), 2.10-1.99 (m, 1H), 1.93-1.84 (m, 1H), 1.18 (d, *J* = 6.3 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 135.0, 129.5, 87.2, 75.7, 71.5, 68.8, 45.3, 38.2, 35.4, 34.8, 20.7, 16.8, 16.0; HRMS (ESI): calcd. for $C_{14}H_{24}O_5Na$ $[M + Na]^+$ 295.1521; found 295.1535.

3.2. Evaluation of the inhibitory activity of mupirocin H for SbnE

A modified malachite green assay was employed for evaluation of the inhibitory activity of mupirocin H against SbnE,[23] a NRPS-independent siderophore synthetase,. To an Eppendorf tube containing 25 mM HEPES, 5 mM $MgCl_2$, 100 µM ATP, 100 µM sodium citrate, 100 µM L-DAP, and 0.001 U/µL inorganic pyrophosphatase (IPP) was added mupirocin H to a final concentration of 50 µM (total volume was 100 µL). DMSO vehicle was used as negative control. The reaction was initiated by addition of SbnE (20 nM) at 37 ºC. The mixture was incubated for 1 h before addition of 25 µL of a quenching solution composed of 50 parts of malachite green solution, 12.5 parts of 7.5% ammonium molybdate, and 1 part of 11% Tween-20 solution. After incubation at 37 ºC for an additional15 min, 100 µL aliquot of each mixture was loaded in a 96-well clear bottom plate and the absorbance at 630 nm was measured using a Hidex Sense microplate reader (Hidex, Finland). A mixture containing the same components except for SbnE was used as a positive control. Data were collected in duplicate.

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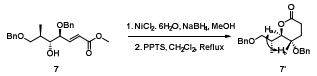
13. The configuration was determined based on the spectroscopic analyses of the δ-lactone **7'** derived from **7** in 2 steps. No correlation between H_a and H_b is observed in NOESY spectrum.



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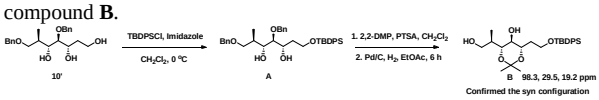
16. Triol **10'** was converted to compound **B** through silyl/acetonide protection and dibenzyl deprotection. Stereochemistry of 1,3-*syn* diol was confirmed by the spectroscopic (^{13}C NMR) analysis of compound **B**.



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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra for all compounds.