EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701748

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701748

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FULL PAPER

Stereoselective total synthesis of non-contiguous polyketide natural product (-)-dolabriferol

Naresh Gantasala,[a,b] Suresh Borra,[a,b] Srihari Pabbaraja*[a,b]

Abstract: Stereoselective total synthesis of non-contiguous polypropionate dolabriferol is accomplished in 17 steps following a divergent and convergent approach. The key reactions involved are enantioselective cross-aldol reaction, aldol dimerization reaction of propionaldehyde, Sharpless asymmetric epoxidation, regioselective epoxide opening and Yamaguchi esterification reaction. Noteworthy is the effect of protecting groups on alcohol substrate for differential reactivity towards Yamaguchi esterification.

Introduction

Investigation of biological and pharmacological properties of the secondary metabolites isolated from marine natural sources has been a subject of great importance. The polyketide natural products attract significant attention due to their remarkable biological and pharmacological activities such as antibiotic, antifungal, anti-cancer, anti-inflammatory and immuno-suppressant etc.[1] In 1996, Gavagnin et al have isolated dolabriferol (**1**) from the skin of the anaspidean mollusk *Dolabrifera dolabrifera*.[2] Though, this compound is assumed to protect the shell-less mollusk from predators, the biological properties of this molecule has not been fully explored. In 2012, structurally related molecules dolabriferol B (**2**) and C (**3**) were isolated from tropical sea hare *Dolabrifera dolabrifera*.[3] Structurally, these natural products are embodied by two polypropionate subunits joined via an unusual C9 acyclic ester linkage which is also a key skeleton of other similar natural products such as baconipyrones A-D[4] (**4**-**7**) and siserrone A[5] (**8**) (Figure 1). Dolabriferol B has the similar skeleton as dolabriferol but has an ethyl moiety inplace of isopropyl moiety at C18. Dolabriferol C has an extended polyketide chain in acid fragment. Though, the structure of dolabriferol was established by extensive NMR experiments and X-ray analysis, the absolute configuration was determined after the total synthesis of dolabriferol by Vogel et al.[6c] The unusual ester linkage and the stereochemistry present in dolabriferols makes it an attractive synthetic target for the synthetic community and several contributions have been well precedented in this regard.[6] Though it is believed that the unusual connectivity might originate from the biosynthetic process, [2] its isolation through a mild base-or acid-catalyzed retro-Claisen rearrangement was not ruled out as the rearrangement proceed *via* an energetically favorable pathway,[7] and further supported by its total synthesis utilizing the retro-Claisen approach.[6a,b] Vogel et al[6c] have reported the first total synthesis of (-)-dolabriferol using Paterson's protocol of esterification wherein a polyketide alicyclic alcohol was coupled with polyketide acid. Attempts to couple hemi-acetal and acid fragment were unsuccessful. However, by taking the enol acetate, the hinderdnes of the alcohol fragment was reduced which gave a promising result for esterification reaction. Goodman et al[6b] have utilized Evan's aldol approach and retro-Claisen rearrangement as the key steps for the total synthesis of (-)-dolabriferol. Ward et al[6a] have accomplished the total synthesis involving an aldol approach and the regioselective retro-Claisen fragmentation approach.

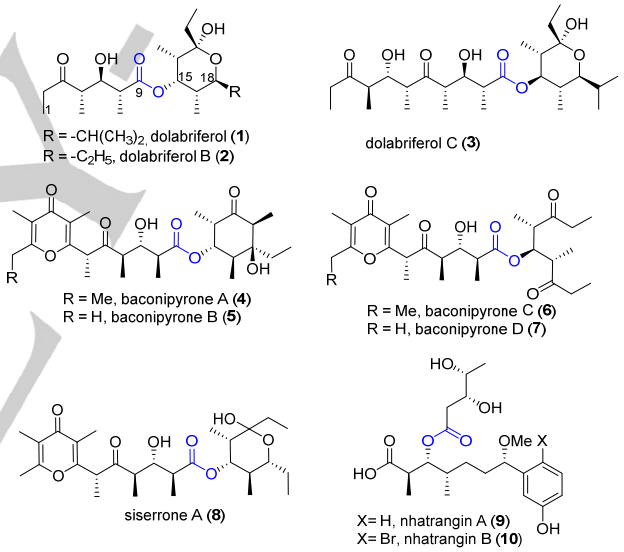

Figure 1. Polyketide/polypropionate natural products.

In continuation to our research interest towards the total synthesis of biologically active natural products,[8] we have recently accomplished the synthesis of nhatrangin A[9] (**7**) wherein a diketide motif (bearing hydroxyl functionality) is attached to 2,3-dihydroxy valeric acid moiety through an ester linkage. Herein we report the total synthesis of dolabriferol employing a divergent cum convergent approach starting from propionaldehyde and involves an esterification reaction as a key reaction.

Results and Discussion

A retrosynthetic analysis of dolabriferol is delineated in Scheme 1. Assuming difficulties for desilylation at last step in earlier

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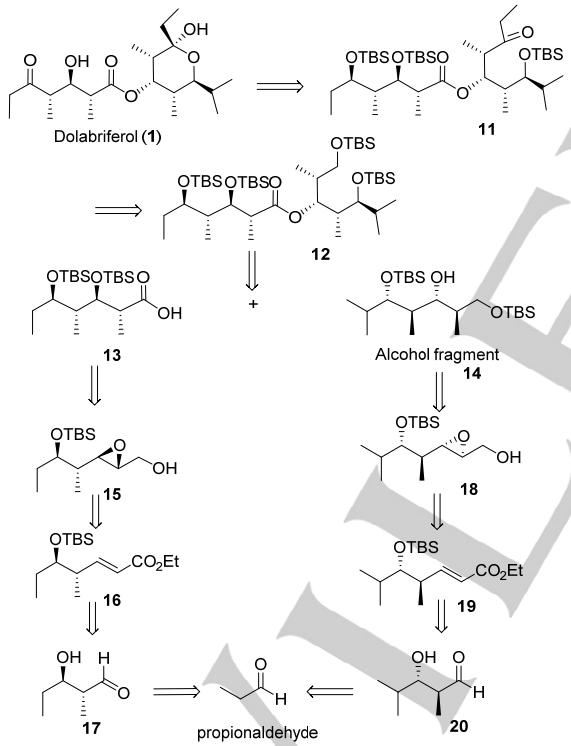
Supporting information for this article is given via a link at the end of the document.

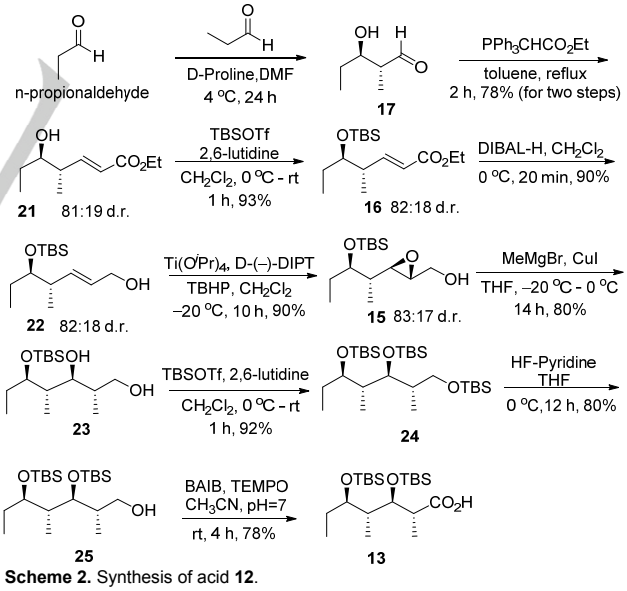
approaches,[6d,f] where in deprotection of silyl moieties proved to be cumbersome as the starting material gets decomposed during deprotection, we slightly modified our key precursor and planned desilylation at the earlier step to overcome such difficulties. Thus, the target molecule **1** could be obtained from **11** by tri-TBS-desilylation to give cyclic hemiketal, which on selective oxidation of C3-secondary alcohol provides the target molecule **1**. **11** can be synthesized from **12** in four-step sequence i.e. by TBS deprotection of primary alcohol, oxidation to aldehyde followed by ethyl Grignard and further oxidation to get the ketone. **12** can be synthesized in a convergent approach by coupling two key fragments, acid **13** and alcohol **14** via an esterification reaction. Both the fragments, acid **13** and alcohol **14** were planned to be independently synthesized starting from readily available propionaldehyde in a divergent fashion. Acid fragment **13** can be synthesized from the corresponding epoxy alcohol **15** through an epoxide ring opening reaction to get 1,3-diol followed by oxidation of primary alcohol to acid functionality with appropriate protection of secondary alcohol. The epoxy alcohol **15** could be derived from α,β-unsaturated ester **16** in two steps i.e ester reduction followed by Sharpless asymmetric epoxidation of allyl alcohol.



Scheme 1. Retrosynthetic analysis of dolabriferol.

Ester **16** can be synthesized from aldehyde **17**, which in turn can be obtained enantioselectively via a self-aldol dimerization of propionaldehyde. The other key fragment alcohol **14** was planned to be synthesized from the epoxy alcohol **18** through a ring opening reaction to yield 1,3-diol followed by TBS protection. The compound **18** can be synthesized from **19** in two steps i.e ester reduction and Sharpless asymmetric epoxidation reaction. The ester **19** in turn can be obtained from aldehyde **20** which could be accessed by a cross-aldol reaction of propionaldehyde and isobutyraldehyde.

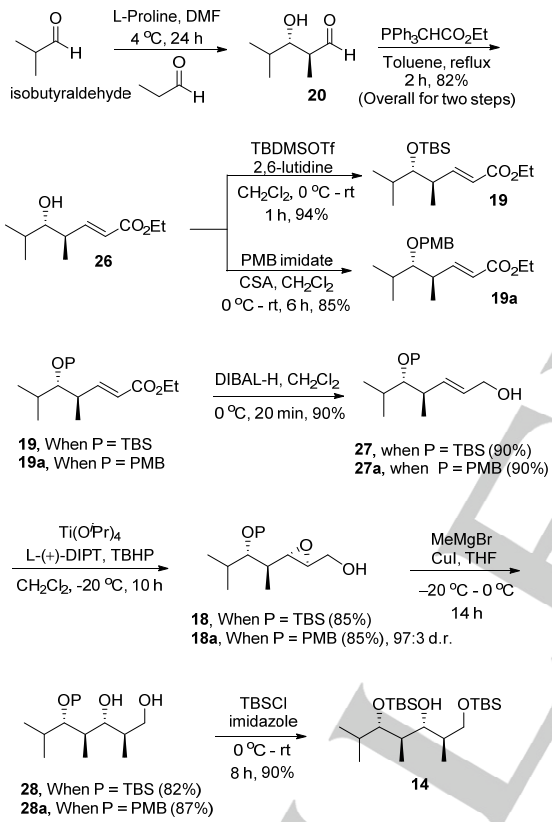
With a strategy of divergent cum convergent approach in mind, the synthesis of acid fragment **13** began with an enantioselective D-proline catalyzed self-aldol addition of propionaldehyde[10] to get the corresponding known α-methyl,β-hydroxyvaleraldehyde **17** as an inseparable (*anti*:*syn* 4.5:1) mixture (as analysed by GCMS, see Supporting Information). With the intention of getting the minor diastereomer separated in the future steps, we proceeded further with the mixture aldehyde **17** embodying a free hydroxyl functionality for a 2C-Wittig homologation with carbethoxy-methylenetriphenylphosphorane to provide α,β-unsaturated ester **21**,[16] which was further treated with TBSOTf to provide the corresponding silyl ether **16**. Reduction of ester **16** with DIBAL-H provided allyl alcohol **22** which was further subjected to Sharpless asymmetric epoxidation[11] reaction to yield the chiral epoxy alcohol **15**. The epoxide ring in **15** was opened with methylmagnesium bromide in presence of copper iodide[12] to provide 1,3-diol **23** which was further masked to its corresponding tri-TBS ether **24** with TBSOTf and 2,6-lutidine. Exposure of trisilylated ether **24** to HF-pyridine afforded primary alcohol **25**, which was oxidized under BAIB and TEMPO conditions[13] to furnish the acid fragment **13** in 78% yield (Scheme 2).



Scheme 2. Synthesis of acid **12**.

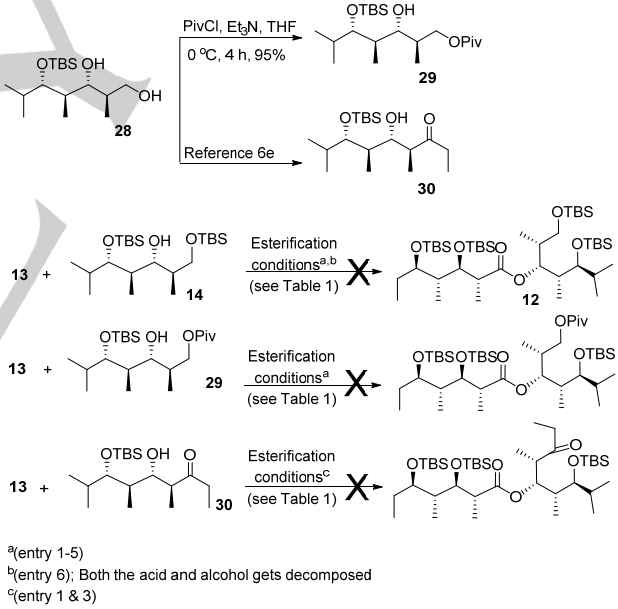
The synthesis of alcohol **14** commenced with a L-proline catalyzed enantioselective cross-aldol reaction[10a] between isobutyraldehyde and propionaldehyde to obtain the corresponding aldol product **20** as an inseparable mixture of *anti*:*syn* mixture in 24.7:1 ratio (as analysed by GCMS, see

Supporting Information). The aldehyde mixture without further purification was subjected to 2C-homologation reaction to provide α,β-unsaturated ester **26**[17] *via* a C2-Wittig olefination reaction. The free 2° alcohol was masked as the corresponding TBS ether **19** and then the ester functionality was reduced with DIBAL-H to provide allyl alcohol **27**. Sharpless asymmetric epoxidation of allyl alcohol **27** with $Ti(O^iPr)_4$ and L-(+)-DIPT with TBHP as oxidizing agent afforded epoxy alcohol **18**. Opening of the epoxy alcohol with methyl magnesium bromide in presence of CuI furnished the methylated 1,3-diol **28**. The primary hydroxyl group of **28** was selectively protected as TBS ether with TBSCl in the presence of imidazole to deliver the key intermediate alcohol fragment **14** in 95% yield (Scheme 3).



Scheme 3. Synthesis of alcohol **13**.

With both the acid **13** and alcohol **14** in hand, the stage was set for an esterification reaction. In our initial attempts under Yamaguchi conditions, when the acid **13** was treated with 2,4,6-trichlorobenzoyl chloride in presence of triethyl amine, a non-polar spot was observed which we believed to be the mixed anhydride (inferring the reactivity of acid functionality). However, after the formation of non-polar spot, when alcohol was added to the reaction mixture, the reaction ended up with disappearance of non-polar spot while the spot corresponding to the alcohol substrate remained intact. Also, after the workup, we could recover back only alcohol **14**. Attempts under various reaction conditions (See Table 1, entry 1-6) by changing several procedures for the coupling reaction did not yield fruitful results. Even under Mitsunobu conditions, to check if the esterification occurs with inversion, it was observed that both the substrates remained intact at room temperature while at 90 °C, both the acid and alcohol fragments gets decomposed. The non-reactivity of alcohol may be attributed to the presence of two bulky TBS moieties which might be hindering the nucleophilic attack of the hydroxyl group onto the active ester. Assuming the reactivity of acid substrate and non-reactivity of alcohol substrate **14**, we focused our attention to investigate further by modifying the protective group of alcohol. Towards this, the compound **28** was converted to pivaloyl ester **29** and treated with acid **13** for an esterification reaction under various conditions (Scheme 4, Table 1, entry 1-5). However, the coupling reaction did not proceed to our expectations and ended up with the recovery of alcohol fragment **29**. We proceeded further to reduce the steric hindrance in alcohol by converting **28** into the known advanced ketone intermediate **30**[6e] which can be used directly for coupling reaction. Our attempts to couple the acid **13** with alcohol **30** were also not fruitful and ended up with either recovery of alcohol or decomposition of both acid and alcohol (Table 1 entry 1-6).



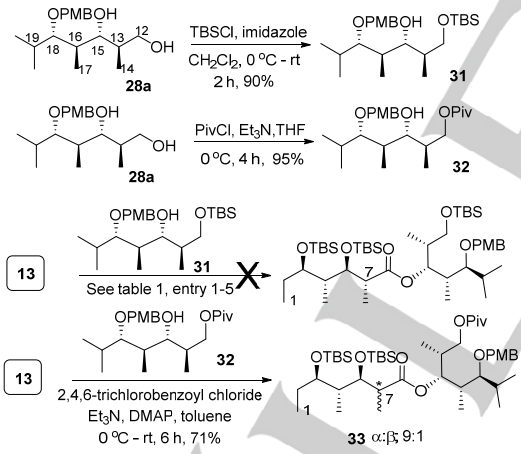
Scheme 4. Synthesis of alcohols **29** and **30**. Coupling of acid **13** with alcohols **14** / **29** / **30**.

Table 1. Conditions attempted for esterification reaction of acid **13** with alcohol **14**/**29**/**30**

Sl. no	Reagents /solvent / temperature	Time	Remarks
1	DCC, DMAP, CH_2Cl_2, 0 °C-rt	10 h	Alcohol recovered
2	EDCI, HOBT, CH_2Cl_2, DIPEA, 0 °C-rt	10 h	Alcohol recovered
3	2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, toluene, 0 °C- rt-70 °C (Yamaguchi conditions)	4-10 h	Alcohol recovered

4	2-methyl nitrobenzoic acid, DMAP, CH_2Cl_2, 0 °C-rt	10 h	Alcohol recovered
5	TPP, DIAD, THF, rt	24 h	Alcohol recovered
6	TPP, DIAD, THF + toluene (1:1), 90 °C	4-10 h	Alcohol and acid decomposed

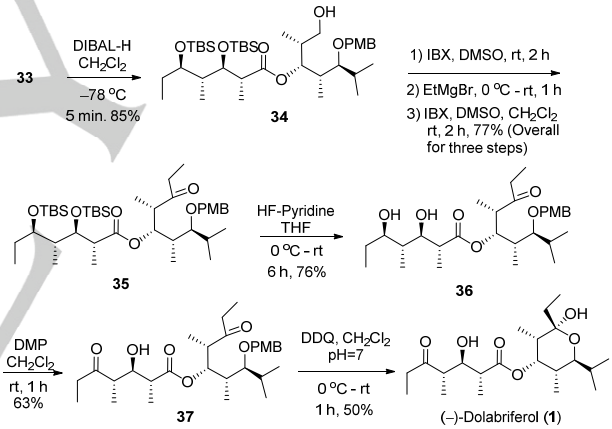
Owing to unsuccessful results from the coupling reaction of acid **13** with alcohols **14** / **29** / **30**, and the positive esterification reaction from the results of Vogel et al[6c] and later by Toste et al,[6d] we further turned our attention for modification of protection group on secondary alcohol (hydroxyl moiety on C18) of **14** to overcome the challenge of esterification reaction. We now investigated through replacement of the secondary silyl moiety with PMB functionality, anticipating in keeping the bulky moiety little farther through a methylene moiety without altering the primary TBS protection at C12. Thus, compound **26** was treated with PMB-imidate to provide the corresponding PMB-ether **19a** in 85% yield. Compound **19a** was treated with DIBAL-H to yield allyl alcohol **27a** and subjected to Sharpless asymmetric epoxidation to provide epoxy alcohol **18a**. Ring opening reaction of **18a** with methylmagnesium bromide in presence of copper iodide furnished the mixture of inseparable 1,2- and 1,3-diols which was further treated with sodium metaperiodate to provide 1,3-diol **28a** (See Scheme 3). Compound **28a** on treatment with TBSCl in presence of imidazole provided the corresponding TBS ether **31**, which was utilized for esterification reaction with acid **13** (Scheme 5). However, once again the reaction was fruitless and ended up with the recovery of alcohol substrate **31**.



Scheme 5. Coupling of acid **13** with alcohols **31** / **32** and synthesis of **33**

In further attempt, the primary hydroxyl moiety (C12 hydroxyl) of **28a** was masked with pivaloyl moiety to yield **32** and then the esterification reaction was attempted. Gratifyingly, the esterification reaction of acid **13** with alcohol **32** proceeded smoothly under Yamaguchi conditions[14,6d] providing the ester **33** (9:1 inseparable diastereomers) in 71% yield.[15] The diastereomer was presumed to be obtained by epimerization at alpha carbon (C7) to carboxylic acid functionality due to exposure to basic conditions (characterized by ^{1}H NMR, See Supporting Information).

With the success of coupling reaction, the rest was to proceed further for the chain extension and ring formation reaction. Towards this, the compound **33** (diastereomeric mixture) was treated with DIBAL-H for pivaloyl deprotection to yield the desired alcohol **34**, which was easily separated from the other diastereomer (minor diastereomer) through column chromatography. Alcohol **34** was oxidized under IBX conditions to yield aldehyde and was treated with ethyl magnesium bromide to yield the secondary alcohol, which was further oxidized under IBX conditions to yield the corresponding ketone **35**. The silyl deprotection at this stage was difficult with TBAF as the reaction resulted in decomposition of the starting material. However, the deprotection challenge was successfully overcome with HF-pyridine to yield diol **36** in 76% yield. Exposure of diol **36** to Dess-Martin periodinane (DMP) provided us the known precursor **37**.[6b] One-pot PMB deprotection and hemiketalization of **37** was easily achieved with DDQ[6b] to furnish the polyketide dolabriferol **1** (Scheme 6). The spectroscopic data of the synthesized compound was found to be identical with that of the reported data.[2]



Scheme 6. Total synthesis of dolabriferol (**1**).

Conclusions

In conclusion, we have accomplished the total synthesis of (-)-dolabriferol in 24 overall steps and seventeen steps in convergent approach starting from commercially available propionaldehyde with 3.0% overall yield (convergent approach). Both the key fragments, acid **13** and alcohol **32** were obtained from propionaldehyde in a divergent fashion. Enantioselective self-aldol dimerization and cross-aldol addition reactions have been successfully employed to secure two chiral centers. Sharpless asymmetric epoxidation reaction has been used to secure third chiral center. The protection groups on alcohol substrate have been found to be crucial towards the esterification reaction. Dolabriferol B (structurally similar molecule) can also be efficiently synthesized employing the above strategy and the efforts for the same are now currently underway in the laboratory.

Experimental Section

General Information. All the reagents were used as received from commercial sources unless otherwise noted. All air and moisture sensitive reactions were conducted under a nitrogen or argon atmosphere using flame-dried or oven-dried glassware with magnetic stirring. CH_2Cl_2 was stirred over CaH_2 and distilled prior to use. Tetrahydrofuran (THF) was dried over Na, benzophenone and distilled prior to use. Toluene was freshly distilled from CaH_2 and used. Reactions were monitored by thin-layer chromatography which was carried out on silica plates (silica gel 60 F254, Merck) using UV-light, iodine and *p*-anisaldehyde for visualization. Column chromatography was carried out using silica gel (60-120 mesh or 100- 200 mesh) packed in glass columns. Technical grade ethyl acetate and petroleum ether were used for column chromatography and were distilled prior to use. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ as solvent on 300 MHz or 400 MHz or 500 MHz spectrometer at ambient temperature. The coupling constant *J* is given in Hz. The chemical shifts (δ) are reported in ppm on scale downfield from TMS and using the residual solvent peak in $CDCl_3$ (H: δ = 7.26 and C: δ = 77.0 ppm) or TMS (δ = 0.0) as internal standard and signal patterns are indicated as follows: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, qd = quartet of doublet, m = multiplet, br = broad, tt = triplet of triplet. IR spectra were recorded on a Bruker Infrared spectrophotometer and are reported as cm^{-1}. High-resolution mass spectra (HRMS) were recorded on a Waters-TOF spectrometer.

(4*S*,5*R*,*E*)-5-Hydroxy-4-methylhept-2-enoate (21)

To a stirred solution of (ethoxycarbonylmethylene)triphenylphosphorane (22.52 g, 64.65 mmol) in toluene (75 mL) under reflux condition was added (2*S*, 3*S*)-3-hydroxy-2,4-dimethylpentanal **17** (5.0 g, 43.103 mmol) in toluene (15 mL) and the resulting mixture was heated at reflux for 2 h. After the reaction was complete, the solvent was removed under reduced pressure to yield crude product, which was then purified by silica gel column chromatography using petroleum ether/EtOAc (7:3) to give α,β unsaturated ester **21**[16] (7.53 g, 78%, diastereoselectivity 81:19) as a colorless oil. $[\alpha]_D^{20}$ = -23.4 (*c* 1.54, $CHCl_3$); IR (Neat): 3447, 2934, 2877, 1702, 1650, 1459, 1370, 1269, 1182, 1097, 975, 865, 754 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 6.95 (dd, *J* = 15.6, 8.2 Hz, 1H), 5.86 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.52–3.42 (m, 1H), 2.47-2.36 (m, 1H), 1.54-1.49 (m, 1H), 1.46-1.35 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 166.5, 150.2, 122.1, 76.1, 60.3, 42.1, 27.4, 15.8, 14.2, 10.0; ESI-HRMS: Calcd *m/z*, for $C_{10}H_{18}O_3Na$: 209.1148 $(M+Na)^+$, found 209.1153.

Ethyl (4*S*,5*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methylhept-2-enoate (16)

To a cold stirred solution of alcohol **21** (5.3 g, 28.49 mmol), in dry CH_2Cl_2 (75 mL) 2,6-lutidine (9.9 mL, 85.48 mmol) and TBSOTf (7.85 mL, 34.19 mmol) were added. After 1 h, the reaction was quenched with sat. NH_4Cl (20 x 3 mL), and the mixture was extracted with CH_2Cl_2 (10 x 3 mL), dried with Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel using petroleum ether/EtOAc (9.5:0.5) to afford TBS ether **16** as a colourless oil (7.95 g, 93%, diastereoselectivity 82:18); $[\alpha]_D^{20}$ = -23.1 (*c* 1.7, $CHCl_3$); IR (Neat): 2958, 2857, 1721, 1652, 1465, 1368, 1253, 1152, 1033, 986, 834, 772, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (dd, *J* = 15.7, 7.9 Hz, 1H), 5.79 (dd, *J* = 15.7, 1.1 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.57-3.49 (m, 1H), 2.52-2.41 (m, 1H), 1.52-1.35 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.87-0.81 (m, 3H), 0.04 (bs, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.7, 151.5, 121.0, 76.5, 60.1, 41.3, 26.8, 25.8, 18.1, 15.1, 14.2, 9.5, -4.3, -4.6; ESI-HRMS: Calcd *m/z*, for $C_{16}H_{32}O_3SiNa$: 323.2018 $(M+Na)^+$, found 323.2023.

(4*R*,5*R*,*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-methylhept-2-en-1-ol (22)

A solution of **16** (6.5 g, 21.66 mmol, 1.0 eq.) in CH_2Cl_2 (65 mL) was cooled to 0 °C, and treated with DIBAL-H (54.16 mmol, 31.8 mL, 1.7 M solution in toluene). After 20 min, the reaction was diluted with CH_2Cl_2 (40 mL) at 0 °C, and the mixture was allowed to warm to room temperature and then quenched with saturated aqueous sodium potassium tartrate solution (40 mL). The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phase occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (20 x 3 mL); The combined organic extracts were washed with saturated aqueous NaCl solution (20 mL), dried over anhydrous Na_2SO_4, and the solvents were evaporated. The crude was purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) to give allyl alcohol **22** (5.03 g, 90%, diastereoselectivity 82:18) as a clear oil. R_f = 0.5 (SiO_2, 30% EtOAc/hexane); $[\alpha]_D^{20}$ = - 12.4 (*c* 1.8, $CHCl_3$); IR (neat): 3330, 2930, 1462, 1376, 1253, 1079, 1059, 927, 938, 863, 790, 771, 666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.75-5.57 (m, 2H), 4.11 (bs, 2H), 3.49-3.41 (m, 1H), 2.37-2.28 (m, 1H), 1.50-1.35 (m, 2H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.04 (bs, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 135.2, 128.8, 77.1, 63.8, 41.2, 26.4, 25.8, 18.1, 16.0, 10.0, -4.3, -4.5; ESI-HRMS: Calcd *m/z*, for $C_{14}H_{30}O_2NaSi$: 281.1907 $(M+Na)^+$, found 281.1904.

((2*R*,3*R*)-3-((2*S*,3*R*)-3-((*tert*-Butyldimethylsilyl)oxy)pentan-2-yl)oxiran-2-yl)methanol (15)

To a solution of $Ti(O^iPr)_4$ (0.75 mL, 2.55 mmol) and 4Å molecular sieves (1.4 g) in CH_2Cl_2 (45 mL), (+)-DIPT (0.53 mL, 2.55 mmol) was added at -20 °C. After 30 min. at this temperature, the solution of allyl alcohol **22** (3.3 g, 12.79 mmol) in dry CH_2Cl_2 (6 mL) was added dropwise. The stirring was continued for additional 30 min and TBHP (7.0 mL, 28.13 mmol, 4M solution in toluene) was added at -20 °C. The mixture was stirred for 10 h at this temperature and filtered. The filtrate was diluted with water (15 mL), 20% aq NaOH Solution (2.5 mL) was added and stirring was continued for 6 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layers were washed with water (2 X 10 mL), dried over anhydrous Na_2SO_4, and evaporated. The crude was purified by silica gel column chromatography using Hexanes/EtOAc (7.5:2.5) to give epoxy alcohol **15** as a clear oil

(3.15 g, 90%, diastereoselectivity 83:17). R_f = 0.4 (SiO_2, 30% EtOAc/hexane); $[\alpha]_D^{20}$ = + 15.4 (*c* 2.3, $CHCl_3$); IR (neat): 3436, 2932, 1464, 1254, 1102, 1010, 939, 835, 760, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 3.96-3.88 (m, 1H), 3.65-3.56 (m, 2H), 2.99 (dd, *J* = 7.4, 2.4 Hz, 1H), 2.92-2.89 (m, 1H), 1.87-1.77 (m, 1H), 1.68-1.61 (m, 1H), 1.57-1.50 (m, 1H), 0.94-0.81 (m, 18H), 0.09-0.02 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 75.9, 62.0, 56.7, 56.3, 39.6, 26.9, 25.8, 18.1, 12.3, 10.1, -4.2, -4.6; ESI-HRMS: Calcd *m/z*, for $C_{14}H_{30}O_3NaSi$: 297.1862 $(M+Na)^+$, found 297.1862.

(2*S*,3*S*,4*S*,5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylheptane-1,3-diol (23)

To a suspension of CuI (0.521 g, 2.73 mmol) in 20 mL of THF at -20 °C was added methyl magnesium bromide in THF (18.24 mL, 27.37 mmol, 1.5 M solution in THF, 3.0 eq.). The resulting yellow-lemon precipitate was cooled to -25 °C and stirring continued for 30 min. Then a solution of epoxide **15** (2.5 g, 9.12 mmol) in THF (6 mL) was added drop wise. The mixture was stirred for 1 h at -25 °C and then warmed to 0 °C and further stirred continuously for 14 h. The reaction was quenched at 0 °C by the careful addition of aqueous NH_4Cl + NH_4OH (1:1 mixture, 18 mL) until the precipitate turned grey and gas evolution was no longer observed. The solids were removed by filtration, rinsed with ethyl acetate, and the combined filtrates were treated with additional saturated aqueous solutions of NH_4Cl + NH_4OH (1:1 ratio, 8 mL) until the aqueous washes were no longer blue in colour. The aqueous phase was then separated, the organic phase was extracted with EtOAc (4 x 8 mL), dried over anhydrous Na_2SO_4, filtered and the solvents were evaporated. The crude was purified by silica gel column chromatography using petroleum ether/EtOAc (7:3) to give the diol **23** as a colorless viscous oil (2.11 g, 80%); R_f = 0.5 (SiO_2, 40% EtOAc/hexane); $[\alpha]_D^{20}$ = - 5.7 (*c* 2.46, $CHCl_3$). Lit. for diastereomer of **23** $[\alpha]_D^{20}$ = +10.2 (*c* 2.5, $CHCl_3$)[6g]; IR (neat): 3354, 2958, 2931, 2851, 1462, 1381, 1255, 1052, 1007, 973, 861, 833, 791, 772, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 4.21 (bs, 1H), 3.91 (dd, *J* = 10.9, 2.7 Hz, 1H), 3.73 (q, *J* = 5.3 Hz, 1H), 3.57 (d, *J* = 10.5 Hz, 1H), 3.49 (dd, *J* = 7.9, 3.6 Hz, 1H), 3.34 (bs, 1H), 1.96-1.85 (m, 1H), 1.86-1.79 (m, 1H), 1.67-1.60 (m, 1H), 1.60-1.53 (m, 1H) 1.11 (d, *J* = 7.0 Hz, 3H), 0.93-0.88 (m, 12H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 81.1, 78.8, 65.4, 39.5, 36.0, 27.4, 25.8, 18.0, 15.3, 14.7, 8.9, -4.3, -4.7; ESI-HRMS: Calcd *m/z*, for $C_{15}H_{35}O_3Si$ $(M+H)^+$: 291.2355, found 291.2361.

(5*R*,6*R*,7*S*,8*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-ethyl-2,2,3,3,6,8,11,11,12,12-decamethyl-4,10-dioxa-3,11 disilatridecane (24)

To a cold stirred solution of diol **23** (1.7 g, 5.86 mmol), 2,6-lutidine (4.07 mL, 35.17 mmol) in dry CH_2Cl_2 (20 mL) and TBSOTf (4.03 mL, 17.58 mmol) were added. After 1 h, the reaction was quenched with sat. NH_4Cl (20 x1 mL), and the mixture was extracted with CH_2Cl_2 (5 x 3 mL), dried with (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel using petroleum ether/EtOAc (9.5:0.5) to afford tri TBS ether **24** as a colourless oil (2.79 g, 92%); $[\alpha]_D^{20}$ = +3.0 (*c* 1.86, $CHCl_3$); IR (neat): 2955, 2931, 2888, 2858, 1467, 1253, 1048, 1007, 832, 769, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 3.82 (ddd, *J* = 8.1, 5.2, 3.1 Hz, 1H), 3.71 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.66 (dd, *J* = 7.3, 3.6 Hz, 1H), 3.39 (dd, *J* = 9.9, 8.1 Hz, 1H), 1.95 – 1.80 (m, 2H), 1.46-1.30 (m, 2H), 0.95 (d, *J* = 7.1 Hz, 3H), 0.91-0.86 (m, 30H), 0.82 (d, *J* = 7.2 Hz, 3H), 0.09-0.01 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 75.1, 73.5, 65.2, 43.0, 40.3, 26.1, 26.0, 25.9, 24.0, 18.3, 18.2, 18.1, 14.2, 10.2, 9.5, -4.0, -4.0, -4.2, -4.3, -5.3, -5.4; ESI-HRMS: Calcd *m/z*, For $C_{27}H_{62}O_3NaSi_3$ $(M+Na)^+$: 541.3904, found 541.3907.

(2*S*,3*S*,4*R*,5*R*)-3,5-bis((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylheptan-1-ol (25)

A solution of HF/pyridine (1.2 mL) was added to a stirred solution of tri TBS ether **24** (2.5 g, 4.82 mmol) in THF (50 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 12 h and then cooled to 0° C and to this was added powdered $NaHCO_3$ portion wise until pH = 7 was attained. After 10 min, the reaction mixture was filtered and concentrated. The crude was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) to afford **25** as a colorless oil (1.55 g, 80% yield). $[\alpha]_D^{20}$ = – 2.0 (*c* 2.49, $CHCl_3$); IR(neat): 3446, 2932, 2858, 1466, 1383, 1255, 1005, 938, 832, 755, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 3.87 (dd, *J* = 6.1, 3.2 Hz, 1H), 3.81 (dt, *J* = 10.8, 3.2 Hz, 1H), 3.75-3.70 (m, 1H), 3.60-3.53 (m, 1H), 2.80 (bs, H), 1.99-1.93 (m, 1H), 1.93-1.87 (m, 1H), 1.50-1.42 (m, 2H), 1.07 (d, *J* = 7.1 Hz, 3H), 0.93-0.86 (m, 24H), 0.11 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 78.1, 73.6, 66.2, 43.4, 36.2, 26.0, 25.9, 25.1, 18.1, 18.1, 16.7, 8.2, -4.0, -4.1, -4.3, -4.6; ESI-HRMS: Calcd *m/z*, For $C_{21}H_{48}O_3NaSi_2$ $(M+Na)^+$: 427.3040, found 427.3103.

(2*R*,3*R*,4*R*,5*R*)-3,5-bis((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylheptanoic acid (13)

BAIB (2.87 g, 8.91 mmol), TEMPO (46.4 mg, 0.29 mmol) were added sequentially to the stirred solution of compound **25** (1.20 g, 2.97 mmol) in acetonitrile buffer solution (P^H = 7) (1:1, 30 mL) at rt and stirred for 4 h. After completion of the reaction, saturated $Na_2S_2O_3$ solution (20 mL) and Et_2O (50 mL) was added and the organic layer was separated. The separated organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to yield the acid **13** (0.968 g, 78% yield) as clear oil. $[\alpha]_D^{20}$ = +1.1 (*c* 0.8, $CHCl_3$); IR(neat): 3405, 2929, 2857, 1706, 1462, 1382, 1252, 1052, 1004, 943, 832, 770, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 4.20 (dd, *J* = 4.2, 1.3 Hz, 1H), 3.63 (dt, *J* = 8.6, 4.0 Hz, 1H), 2.62 (qd, *J* = 7.3, 1.3, 7.2 Hz, 1H), 2.00-1.89 (m, 1H), 1.55-1.50 (m, 2H), 1.32 (d, *J* = 7.3 Hz, 3H), 0.96 (s, 9H), 0.90 (s, 9H), 0.86-0.82 (m, 6H), 0.17 (s, 6H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 176.6, 75.8, 73.1, 42.5, 40.1, 25.8, 25.7, 25.6, 18.0, 17.9, 17.2, 9.1, 6.5, -4.0, -4.3, -4.8, -4.8; ESI-HRMS: Calcd *m/z*, For $C_{21}H_{46}O_4NaSi_2$ $(M+Na)^+$: 441.2832, found 441.2811.

Ethyl (4*R*,5*S*,*E*)-5-hydroxy-4,6-dimethylhept-2-enoate(26)

To a stirred solution of (ethoxycarbonylmethylene)triphenylphosphorane (8.03 g, 23.07 mmol) in toluene (40 mL) under reflux condition was added (2*S*,

3*S*)-3-hydroxy-2,4-dimethylpentanal **20** in toluene (2.0 g, 15.38 mmol) and the resulting mixture was heated at reflux for 2 h. After the reaction was complete, the solvent was removed under reduced pressure to yield crude product, which was then purified by silica gel column chromatography using petroleum ether/EtOAc (7:3) to give α,β-unsaturated ester **26**[17] (2.95 g, 82%) as a colorless oil. $[\alpha]_D^{20}$ = +23.5 (*c* 0.2, $CHCl_3$), Lit. $[\alpha]_D^{20}$ = +19.1 (*c* 1.04, $CHCl_3$)[17]; IR (Neat): 3503, 2970, 1711, 1650, 1460, 1373, 1241, 1181, 1100, 1041, 987, 862, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.00 (dd, *J* = 15.8, 8.5 Hz, 1H), 5.88 (dd, *J* = 15.9, 0.7 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.20 (dd, *J* = 10.0, 5.1 Hz, 1H), 2.54 (tq, *J* = 13.9, 6.9 Hz, 1H), 1.73 (td, *J* = 13.2, 6.6 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 166.5, 150.4, 122.1, 79.8, 60.2, 39.8, 30.9, 19.5, 17.0, 16.8, 14.2; ESI-HRMS**:** Calcd *m/z* for $C_{11}H_{21}O_3(M+H)^+$; 201.1493, found 201.1485.

(4*R*,5*S*,*E*)-Ethyl 5-((*tert*-butyldimethylsilyl)oxy)-4,6-dimethylhept-2-enoate (19)

To a cold stirred solution of alcohol **26** (1.2 g, 6.0 mmol), 2,6-lutidine (1.8 mL, 15.6 mmol) in anhydrous CH_2Cl_2 (20 mL) and TBSOTf (1.79 mL, 7.8 mmol) were added. After 1 h, the reaction was quenched with sat. NH_4Cl (1 x 8 mL), and the mixture was extracted with CH_2Cl_2 (4 x 3 mL), dried with (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel using petroleum ether/EtOAc (9.5:0.5) to afford TBS ether **19** as a colourless oil (1.77 g, 94%); $[\alpha]_D^{20}$ = + 13.3 (*c* 0.97, $CHCl_3$), Lit. for C4-epimer, $[\alpha]_D^{25}$ = - 27.0 (*c* 1.5, CH_2Cl_2)[18] ; IR (Neat): 2960, 2933, 2858, 1718, 1652, 1467, 1370, 1253, 1153, 1040, 840, 758, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.05 (dd, *J* = 15.7, 8.1 Hz, 1H), 5.77 (dd, *J* = 15.8, 1.2 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.36 (t, *J* = 4.7 Hz, 1H), 2.57-2.48 (m, 1H), 1.78-1.70 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.91(s, 9H), 0.87 (dd, *J* = 6.7, 4.5 Hz, 6H), 0.04 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 152.5, 120.4, 80.4, 60.0, 40.7, 32.2, 26.0, 19.7, 18.3, 18.0, 17.3, 14.2, -3.7, -3.8. ESI-HRMS: Calcd *m/z*, for $C_{17}H_{34}O_3NaSi$: 337.2175 $(M+Na)^+$, found 337.2146.

(4*R*,5*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-4,6-dimethylhept-2-en-1-ol (27)

A solution of **19** (2.3 g, 7.32 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C, and treated with DIBAL-H (18.31 mmol, 10.77 mL, 1.7 M solution in toluene). After 20 min, the reaction was diluted with CH_2Cl_2 (18 mL) at 0 °C, and the mixture was allowed to warm to room temperature and then quenched with saturated aqueous Na+/K+-tartrate solution (18 mL). The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phase was observed. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (8 x 3 mL); The combined organic extracts were washed with saturated aqueous NaCl solution (8 mL), dried over anhydrous Na_2SO_4, and the solvents were evaporated. The crude was purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) to give allyl alcohol **27** (1.79 g, 90%) as a clear oil. $[\alpha]_D^{20}$ = +1.6 (*c* 1.7, $CHCl_3$). Literature for C4-epimer $[\alpha]_D^{25}$ = +10.6 (*c* 0.5, $CHCl_3$)[19]; IR (neat): 3341, 2957, 2929, 2857, 1462, 1362, 1253, 1183, 1052, 1005, 974, 834, 769, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.77-5.71 (m, 1H), 5.62-5.55 (m, 1H), 4.10 (t, *J* = 5.1 Hz, 2H), 3.28 (dd, *J* = 5.1, 4.1 Hz, 1H), 2.42-2.34 (m, 1H), 1.77-1.69 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.87 (dd, *J* = 6.7, 5.7 Hz, 6H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 128.1, 80.9, 64.0, 40.6, 32.1, 26.1, 20.0, 18.4, 18.3, -3.7, -3.7; ESI-HRMS: Calcd *m/z*, for $C_{15}H_{32}O_2NaSi$:295.2069 $(M+Na)^+$, found 295.2063.

((2*R*,3*R*)-3-((2*S*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4-methylpentan-2-yl)oxiran-2-yl)methanol (18)

To a solution of $Ti(O^iPr)_4$ (0.43 mL, 1.47 mmol) and 4 Å molecular sieves (0.8 g) in CH_2Cl_2 (25 mL), (+)-DIPT (0.30 mL, 1.47 mmol) was added at -20 °C. After 30 min at this temperature, a solution of allyl alcohol **27** (2.0 g, 7.35 mmol) in dry CH_2Cl_2 (4 mL) was added drop wise. The stirring was continued for additional 30 min and TBHP (16.17 mmol, 4.04 mL, 4M solution in toluene) was added at -20 °C. The mixture was stirred for 10 h at this temperature and filtered. The filtrate was diluted with water (8.6 mL), 20% aq NaOH Solution (1.5 mL) was added and stirring was continued for 6 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 6 mL). The combined organic layers were washed with water (2 x 5 mL), dried over anhydrous Na_2SO_4, and evaporated. The crude was purified by silica gel column chromatography using Hexanes/EtOAc (8:2) to give epoxy alcohol **18**, as a clear oil (1.8 g, 85%): R_f = 0.5 (SiO_2, 30% EtOAc/hexane); $[\alpha]_D^{20}$ = - 10.7 (*c* 0.58, $CHCl_3$); IR (neat): 3419, 2957, 2932, 2858, 1466, 1384, 1253, 1105, 1050, 972, 835, 769, 672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.92 (ddd, *J* = 12.5, 8.0, 2.5 Hz, 1H), 3.62-3.56 (m, 1H), 3.41 (dd, *J* = 5.9, 3.2 Hz, 1H), 3.07 (dd, *J* = 7.1, 2.4 Hz, 1H), 2.92 (dq, *J* = 4.8, 2.5 Hz, 1H), 1.95-1.85 (m, 1H), 1.72-1.68 (m, 1H), 0.95 (d, *J* = 2.8 Hz, 3H), 0.94 (d, *J* = 3.2 Hz, 3H), 0.93-0.91 (m, 12H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 80.0, 62.1, 56.9, 56.7, 38.9, 32.3, 26.1, 19.4, 19.0, 18.3, 14.4, -3.8, -3.9; ESI-HRMS: Calcd *m/z*, for $C_{15}H_{32}O_3NaSi$: 311.2022 $(M+Na)^+$, found 311.2018.

(2*S*,3*S*,4*S*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethylheptane-1,3-diol (28)

To a suspension of CuI (0.258 g, 1.35 mmol) in 10 mL of THF at -20 °C was added methyl magnesium bromide in THF (13.54 mmol, 9.0 mL (1.5 M solution in THF)). The resulting yellow-lemon precipitate was cooled to -25 °C and stirring continued for 30 min. Then a solution of epoxide **18** (1.3 g, 4.51 mmol) in THF (4 mL) was added dropwise. The mixture was stirred for 1 h at -25 °C and then warmed to 0 °C and further stirred continuously for 14 h. The reaction was quenched at 0 °C by the careful addition of aqueous NH_4Cl + NH_4OH (1:1 ratio, 8 mL) until the precipitate turned grey and gas evolution was no longer in observed. The solids were removed by filtration, rinsed with ethyl acetate, and the combined filtrates were treated with additional aqueous NH_4Cl + NH_4OH (1:1 ratio, 6 mL) until the aqueous washes were no longer blue in color. The aqueous phase was then separated, the organic phase was extracted with EtOAc (4 x 4 mL), dried over anhydrous Na_2SO_4 and the solvents were evaporated, The crude was purified by silica gel column chromatography using petroleum ether/EtOAc (7:3) to give the diol **28** as a colorless viscous oil (1.12 g, 82%);

R_f = 0.5 (SiO_2, 30% EtOAc/hexane); $[\alpha]_D^{20}$ = + 5.4 (*c* 0.69, $CHCl_3$); IR (neat): 3392, 2957, 2882, 1741, 1684, 1581, 1462, 1373, 1250, 1106, 1044, 975, 834, 771, 675, 607 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.68-3.63 (m, 3H), 3.55 (dd, *J* = 9.1, 1.8 Hz, 1H), 1.93-1.88 (m, 1H), 1.86-1.80 (m, 2H), 0.94 (d, *J* = 4.5 Hz, 3H), 0.93 (d, *J* = 4.7 Hz, 3H), 0.92 (s, 9H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.12 (s, 3H), 0.11 (s. 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 82.0, 81.3, 68.7, 37.4, 36.4, 32.8, 29.6, 26.0, 18.6, 18.4, 13.6, 7.7, -3.2, -4.2. ESI-HRMS: Calcd *m/z*, for $C_{16}H_{36}O_3NaSi$ $(M+Na)^+$: 327.2333, found 327.2331.

(5*R*,6*S*,7*S*,8*S*)-5-isopropyl-2,2,3,3,6,8,11,11,12,12-decamethyl-4,10-dioxa-3,11-disilatridecan-7-ol (14)

To a cold stirred solution of alcohol **28** (1.0 g, 3.28 mmol), imidazole (0.671 g, 9.86 mmol) and TBSCl (0.743 g, 4.93 mmol) in dry CH_2Cl_2 (20 mL) were added. After 4 h, the reaction was quenched with sat. NH_4Cl (10 x 1 mL), and the mixture was extracted with CH_2Cl_2 (2 x 3 mL), dried with (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel using petroleum ether/EtOAc (9.5:0.5) to afford TBS ether **14** as a colourless oil (1.23 g, 90%); $[\alpha]_D^{20}$ = - 12.2 (*c* 2.27, $CHCl_3$); IR (Neat): 3504, 2956, 2885, 1470, 1362, 1256, 1042, 988, 833, 771, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.75 (dd, *J* = 9.9, 4.2 Hz, 1H), 3.67-3.60 (m, 1H), 3.57 (dd, *J* = 7.7, 4.5 Hz, 1H), 3.55-3.51 (m, 2H), 1.99-1.91 (m, 1H), 1.85-1.75 (m, 1H), 1.73-1.64 (m, 1H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.8 Hz,, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.08 (s, 6H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 78.9, 77.4, 68.8, 38.6, 37.6, 31.1, 26.2, 25.8, 20.4, 18.5, 18.2, 16.5, 13.3, 9.6, -3.3, -3.5, -5.5, -5.6; ESI-HRMS: Calcd *m/z*, for $C_{22}H_{51}O_3Si_2$: 419.3377 $(M+H)^+$, found 419.3374.

(2*R*,3*R*,4*R*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-2,4,6-trimethylheptyl pivalate (29)

To a cooled solution of diol **28** (500 mg, 1.64 mmol) in CH_2Cl_2 (20 mL) were added successively pivaloyl chloride (0.26 mL, 2.13 mmol) and Et_3N (0.45 mL, 3.28 mmol) at 0° C and the mixture was stirred at 0° C for 4 h. The resulting reaction mixture was then poured into ice-water (5 mL), warmed to rt and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel column chromatography using Hexanes/EtOAc (9:1) to afford alcohol **29** as a colorless oil (0.606 g, 95%); $[\alpha]_D^{20}$ = + 8.1 (*c* 1.71, $CHCl_3$); IR (neat): 3153, 2961, 1708, 1467, 1390, 1289, 1162, 1042, 973, 834, 772, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.29 (dd, *J* = 10.8, 5.2 Hz, 1H), 4.10 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.60 (t, *J* = 4.1 Hz, 1H), 3.30 (d, *J* = 9.2 Hz, 1H), 1.94-1.83 (m, 2H), 1.82-1.71 (m, 1H), 1.21 (s, 9H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.92-0.88 (m, 15H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0, 80.2, 74.9, 66.8, 38.9, 36.7, 32.1, 27.2, 26.1, 19.3, 18.3, 17.5, 13.9, 8.3, -3.3, -4.0; ESI-HRMS: Calcd *m/z*. for $C_{21}H_{44}O_4NaSi$: 411.2907 $(M+Na)^+$, found 411.2912.

Ethyl (4*R*,5*S*,*E*)-5-((4-methoxybenzyl)oxy)-4,6-dimethylhept-2-enoate (19a)

To a stirred solution of alcohol **26** (2.0 g, 10.0 mmol), freshly prepared 4-methoxybenzyl trichloroacetimidate (4.23 g, 15.0 mmol), and CH_2Cl_2 (30 mL) in a 100-mL round bottom flask, under an atmosphere of N_2, was added (±)-camphor-10-sulfonic acid (0.464 g, 2.0 mmol) in one portion at 0 °C. The reaction was allowed to stirr for 6 h at rt. After complete consumption of starting material, the reaction mixture was quenched with aq $NaHCO_3$ (15 mL) and diluted with water (10 mL). The aqueous phase was then separated, the organic phase was extracted with CH_2Cl_2 (2 x 10 mL) and dried over anhydrous Na_2SO_4), and the organic layers were evaporated. The crude was purified by silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5) to give PMB ether **19a** (2.72 g, 85% yield) as a colorless oil. $[\alpha]_D^{20}$ = +2.1 (*c* 1.03, $CHCl_3$); IR (neat): 2962, 1715, 1513, 1462, 1299, 1245, 1175, 1155, 1082, 1032, 993, 801 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.30-7.24 (m, 2H), 7.08 (dd, *J* = 15.8, 8.4 Hz, 1H), 6.89-6.85 (m, 2H), 5.82 (dd, *J* = 15.7, 0.9 Hz, 1H), 4.48 (s, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 3.01 (dd, *J* = 5.9, 5.3 Hz, 1H), 2.67-2.59 (m, 1H), 1.82 (dq, *J* = 13.4, 6.7 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.7, 159.1, 151.6, 130.8, 129.3, 121.0, 113.7, 88.1, 74.7, 60.1, 55.2, 39.7, 31.2, 19.8, 18.0, 17.0, 14.3; ESI-HRMS: Calcd *m/z* for $C_{19}H_{28}O_4Na$ $(M+Na)^+$; 343.1885, found 343.1886.

(4*R*,5*S*,*E*)-5-((4-Methoxybenzyl)oxy)-4,6-dimethylhept-2-en-1-ol (27a)

A solution of **19a** (2.0 g, 6.25 mmol, 1.0 eq.) in CH_2Cl_2 (30 mL) was cooled to 0 °C, and treated with DIBAL-H (9.19 mL, 15.62 mmol (1.7 M solution in toluene)). After 20 min. the reaction was diluted with CH_2Cl_2 (15 mL) at 0 °C, and the mixture was allowed to warm to room temperature and then quenched with saturated aqueous sodium potassium tartrate solution (20 mL). The resulting mixture was vigorously stirred until a clear separation of both organic and aqueous phase occurred. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 x 3 mL); The combined organic extracts were washed with saturated aqueous NaCl solution (5 mL), dried over anhydrous Na_2SO_4, and the solvents were evaporated. The crude was purified by silica gel column chromatography using petroleum ether/EtOAc (7.5:2.5) to give allyl alcohol **27a** (1.56 g, 90%) as a clear oil. $[\alpha]_D^{20}$ = - 12.4 (*c* 1.36, $CHCl_3$); IR(Neat): 3405, 2961, 2869, 1612, 1513, 1461, 1354, 1300, 1245, 1174, 1067, 1034, 974, 819, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.30-7.26 (m, 2H), 6.89-6.84 (m, 2H), 5.75 (dd, *J* = 15.5, 8.1 Hz, 1H), 5.64 (dd, *J* = 15.5, 9.8 Hz, 1H), 4.50 (s, 2H), 4.06 (d, *J* = 5.7 Hz, 2H), 3.79 (s, 3H), 2.93 (dd, *J* = 6.7, 4.6 Hz, 1H), 2.53-2.43 (m, 1H), 1.81 (dq, *J* = 13.4, 6.7 Hz,1H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 158.9, 135.2, 131.0, 129.1, 128.7, 113.5, 88.7, 74.7, 63.7, 55.1, 39.5, 31.1, 19.8, 18.2, 18.1; ESI-HRMS: Calcd *m/z* for $C_{17}H_{26}O_3Na$ $(M+Na)^+$: 301.1780, found 301.1769.

((2*S*,3*S*)-3-((2*S*,3*S*)-3-((4-Methoxybenzyl)oxy)-4-methylpentan-2-yl)oxiran-2-yl)methanol (18a)

To a solution of Ti(*O*^{i}*Pr*)$_4$ (0.42 mL, 1.43 mmol) and 4Å molecular sieves (0.79 g) in CH_2Cl_2 (30 mL), (+)-DIPT (0.30 mL, 1.43 mmol)

was added at -20 °C. After 30 min at this temperature, a solution of allyl alcohol **27a** (2.0 g, 7.19 mmol) in dry CH_2Cl_2 (4 mL) was added drop wise. The stirring was continued for additional 30 min and TBHP (3.9 mL, 4M solution in toluene) was added at -20 °C. The mixture was stirred for 10 h at this temperature and filtered. The filtrate was diluted with water (8.6 mL), 20% aq NaOH Solution (1.5 mL) was added and stirring was continued for 6 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL), dried over anhydrous Na_2SO_4, and evaporated. The crude was purified by silica gel column chromatography using Hexanes/EtOAc (8:2) to give epoxy alcohol **18a** as a clear oil (1.79 g, 85%, diastereoselectivity 97:3): $[\alpha]_D^{20}$ = - 15.2 (*c* 1.37, $CHCl_3$); IR(neat): 3422, 2927, 1612, 1513, 1461, 1383, 1300, 1245, 1175, 1062, 1034, 967, 922, 890, 818, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.32-7.27 (m, 2H), 6.90-6.86 (m, 2H), 4.53 (q, *J* = 10.6 Hz, 2H), 3.88 (dd, *J* = 12.3, 2.7 Hz, 1H), 3.80 (s, 3H), 3.59 (dd, *J* = 12.3, 4.4 Hz, 1H), 3.10 (dd, *J* = 7.2, 2.3 Hz, 1H), 3.05 (dd, *J* = 7.1, 4.1 Hz, 1H), 2.91 (dt, *J* = 2.5, 4.7 Hz, 1H), 2.03 (dq, *J* = 13.7, 6.8 Hz, 1H), 1.84-1.76 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 3.9 Hz, 3H), 0.97 (d, *J* = 3.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.1, 131.0, 129.2, 113.7, 88.1, 74.8, 62.1, 57.1, 56.2, 55.2, 37.8, 31.4, 19.9, 18.7, 14.1; ESI-HRMS: Calcd for $C_{17}H_{26}O_4Na$ $(M+Na)^+$: 317.1729, found 317.1712.

(2*R*,3*R*,4*R*,5*S*)-5-((4-Methoxybenzyl)oxy)-2,4,6-trimethylheptane-1,3-diol (28a)

To a suspension of CuI (0.641 g, 3.36 mmol) in 30 mL of THF at -20 °C was added methyl magnesium bromide in THF (22.44 mL, 33.67 mmol, 1.5 M solution in THF, 3.0 eq.). The resulting yellow-lemon precipitate was cooled to -25 °C and stirring continued for 30 min. Then a solution of epoxide **18a** (3.3 g, 11.22 mmol) in THF (14 mL) was added dropwise. The mixture was stirred for 1 h at -25 °C and then warmed to 0 °C and further stirred continuously for 14 h. The reaction was quenched at 0 °C by the careful addition of saturated aqueous NH_4Cl + NH_4OH (1:1 ratio, 30 mL) until the precipitate turned grey and gas evolution was no longer in observed. The solids were removed by filtration, rinsed with ethyl acetate, and the combined filtrates were treated with additional aqueous NH_4Cl + NH_4OH (1:1 ratio, 12 mL) until the aqueous washes were no longer blue in color. The aqueous phase was then separated, the organic phase was extracted with EtOAc (4 x 10 mL), dried over anhydrous Na_2SO_4 and the solvents were evaporated. The crude mixture (1,2 and 1,3-diol) was analysed with LCMS to show the presence of 1,3 and 1,2-diols in 91.5:8.5 ratio. The crude mixture (dissolved in THF:H_2O (3:1 ratio, 40 mL) was treated with $NaIO_4$ to oxidatively cleave the 1,2-diol product leaving the 1,3-diol intact. After the filtration, the reaction mixture was quenched with aqueous solution of $NaHCO_3$ and extracted with ethyl acetate. Evaporation of the solvent followed by silica gel column chromatography using petroleum ether/EtOAc (7:3) afforded diol **28a** as a colorless viscous oil (3.02 g, 87%); $[\alpha]_D^{20}$ = + 29.89 (*c* 0.91, $CHCl_3$); IR (neat): 3386, 2961, 2931, 2874, 1612, 1513, 1462, 1382, 1300, 1246, 1175, 1029, 971, 817, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.30-7.23 (m, 2H), 6.91-6.86 (m, 2H), 4.64 (bs, 1H), 4.58 (q, *J* = 10.5 Hz, 2H), 3.91 (dd, *J* = 10.8, 1.6 Hz, 1H), 3.80 (s, 3H), 3.57 (dd, *J* = 10.8, 1.6 Hz, 1H), 3.55-3.50 (m, 1H), 3.43 (bs, 1H), 3.22 (dd, *J* = 7.0, 3.9 Hz, 1H), 2.03-1.94 (m, 2H), 1.85-1.80 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 159.3, 129.8, 129.4, 113.8, 90.9, 80.5, 75.2, 64.9, 55.2, 38.9, 35.6, 31.7, 20.6, 16.9, 16.3, 15.5; ESI-HRMS: Calcd *m/z*, for $C_{18}H_{30}O_4Na$: 333.2042 $(M+Na)^+$, found 333.2045.

(2*R*,3*R*,4*R*,5*S*)-1-((*tert*-butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptan ol (31)

To a cold stirred solution of alcohol **28a** (1.0 g, 3.22 mmol), imidazole (0.658 g, 9.67 mmol) and TBSCl (0.729 g, 4.83 mmol) in dry CH_2Cl_2 (25 mL) were added. After 2 h, the reaction was quenched with sat. NH_4Cl (8 x 1 mL), and the mixture was extracted with CH_2Cl_2 (2 x 4 mL), dried with (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel using petroleum ether/EtOAc (9.5:0.5) to afford TBS ether **31** as a colourless oil (1.23 g, 90%); R_f = 0.5 (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{20}$ = + 14.3 (*c* 0.30, $CHCl_3$); IR (neat): 3498, 2930, 2857, 1613, 1513, 1463, 1362, 1247, 1072, 1036, 988, 833, 774, 754, 667 cm^{-}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.29-7.25 (m, 2H), 6.88-6.84 (m, 2H), 4.61 (d, *J* = 10.8 Hz, 1H), 4.51 (d, *J* = 10.9 Hz, 1H), 4.05 (d, *J* = 3.9 Hz, 1H), 3.80 (s, 3H), 3.71-3.63 (m, 2H), 3.50-3.46 (m, 1H), 3.38 (dd, *J* = 6.4, 3.9 Hz, 1H), 2.08-2.00 (m, 1H), 1.99-1.90 (m, 1H), 1.01 (t, *J* = 6.5 Hz, 6H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 131.0, 129.0, 113.6, 87.3, 79.4, 73.7, 66.0, 55.2, 39.1, 36.7, 30.8, 25.8, 21.1, 18.1, 17.2, 15.3, 15.0, -5.5; ESI-HRMS: Calcd *m/z*, for $C_{24}H_{44}O_4SiNa$: 447.2907 $(M+Na)^+$, found 447.2895.

(2*R*,3*R*,4*R*,5*S*)-3-Hydroxy-5-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptyl pivalate (32)

To a cooled solution of diol **28a** (1.0 g, 3.22 mmol) in CH_2Cl_2 (25 mL) were added successively pivaloyl chloride (0.47 mL, 3.87 mmol) and Et_3N (0.67 mL, 4.83 mmol) at 0 ºC and the mixture was stirred at 0 ºC for 4 h. The resulting reaction mixture was then poured into ice-water (5 mL), warmed to rt and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by silica gel column chromatography using Hexanes/EtOAc (9:1) to afford alcohol **32** as a colorless oil (1.2 g, 95%); $[\alpha]_D^{20}$ = +38.54 (*c* 1.30, $CHCl_3$); IR (neat): 3480, 2965, 1721, 1621, 1514, 1465, 1368, 1289, 1246, 1161, 1034, 982, 820, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.29-7.24 (m, 2H), 6.90-6.84 (m, 2H), 4.58 (s, 2H), 4.30 (dd, *J* = 11.0, 5.1 Hz, 1H), 4.04 (bs, 1H), 3.91 (dd, *J* = 10.9, 7.9 Hz, 1H), 3.80 (s, 3H), 3.47 (dt, *J* = 8.5, 1.7 Hz, 1H), 3.20 (dd, *J* = 7.3, 3.5 Hz, 1H), 2.14-2.04 (m, 1H), 2.00-1.93 (m, 1H), 1.93-1.86 (m, 1H), 1.19 (s, 9H), 1.05 (dd, *J* = 8.8, 6.9 Hz, 6H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 178.7, 159.3, 130.1, 129.4, 113.8, 90.6, 77.9, 74.9, 65.5, 55.2, 38.8, 38.7, 34.6, 31.6, 27.2, 20.7, 16.7, 16.0, 15.9; ESI-HRMS: Calcd *m/z*. for $C_{23}H_{38}O_5Na$: 417.2617 $(M+Na)^+$, found 417.2615.

(2*R*,3*R*,4*S*,5*S*)-5-((4-Methoxybenzyl)oxy)-2,4,6-trimethyl-1-(pivaloyloxy)heptan-3-yl (2*R*,3*R*,4*R*,5*R*)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylheptanoate (33)

A stirred solution of alcohol **32** (500 mg, 1.26 mmol) and acid **13** (583 mg, 1.39 mmol) in anhydrous toluene (15 mL) was treated with Et_3N (0.53 mL, 3.80 mmol), DMAP (0.775 g, 6.34 mmol) and 2,4,6-trichlorobenzoyl chloride (0.39 mL, 2.53 mmol) at 0 ºC. The resulting white suspension was stirred at rt for 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (7.5 mL) at 0 ºC and diluted with water (5 mL). The reaction mixture was extracted with ethyl acetate (3 x 6 mL) and the combined organic extracts were washed with water (5 mL) and brine (5 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give the crude product which was purified by silica gel column chromatography (hexanes/EtOAc) to afford inseparable diastereomeric mixture of ester **33** (0.715 g, 71%) as a colorless oil. (The diastereomer was observed due to epimerization at C7 in **33** under basic conditions (TEA, DMAP) which was confirmed by the ^{1}H NMR of the crude product. The diastereomeric ratio was found to be 9:1 by LCMS analysis (this was also in consistence with ^{1}H NMR data). R_f = 0.5 (SiO_2, 10% EtOAc/hexane); $[\alpha]_D^{20}$ = +32.0, (*c* 1.05, $CHCl_3$); IR (Neat): 2958, 2930, 2857, 1729, 1613, 1514, 1362, 1250, 1156, 1066, 1005, 938, 833, 754, 666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.29-7.23 (m, 2H), 6.87-6.84 (m, 2H), 5.10 (t, *J* = 5.2 Hz, 1H), 4.58 (d, *J* = 10.7, Hz, 1H), 4.48 (d, *J* = 10.7, Hz, 1H), 4.19 (dd, *J* = 10.9, 3.9, Hz, 1H), 4.14 (dd, *J* = 9.7, 2.9 Hz, 1H), 3.88-3.85 (m, 1H), 3.85-3.81 (m, 1H), 3.80 (s, 3H), 3.17 (dd, *J* = 6.5, 4.4, Hz, 1H), 2.68 (qd, *J* = 7.1, 2.8,7.2 Hz, 1H), 2.43-2.33 (m, 1H), 2.27-2.17 (m, 1H), 1.93-1.83 (m, 2H), 1.41-1.28 (m, 2H), 1.26-1.19 (m, 12H), 1.01 (dd, *J* = 7.2, 4.7 Hz, 6H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.91-0.88 (m, 21H), 0.71 (d, *J* = 7.2 Hz, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.06-0.03, (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 178.3, 175.2, 158.9, 131.1, 128.8, 113.6, 84.8, 77.3, 73.7, 73.2, 72.8, 65.7, 55.2, 43.2, 42.7, 38.7, 37.6, 34.7, 30.3, 27.1, 26.1, 25.9, 25.1, 21.1, 18.4, 18.1, 17.5, 15.6, 13.7, 12.0, 11.7, 9.6, -3.7, -4.3, -4.4, -4.5; ESI-HRMS: Calcd *m/z*, For $C_{44}H_{83}O_8Si_2$ $(M+H)^+$: 795.5626, found 795.5624.

(2*R*,3*R*,4*R*,5*R*)-(2*R*,3*R*,4*S*,5*S*)-1-Hydroxy-5-((4-methoxybenzyl)oxy)-2,4,6-trimethylheptan-3-yl 3,5-bis((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylheptanoate (34)

A solution of pivolate **33** (0.65 g, 0.818 mmol) (diastereomeric mixture) in CH_2Cl_2 (25 mL) was cooled to -78 ºC and DIBAL-H (1.0 mL, 1.80 mmol 1.7 M in toluene, 2.2 equiv) was added drop wise. After 5 min, the reaction was diluted with CH_2Cl_2 (5 mL) at 0 °C, and the mixture was allowed to warm to room temperature and then quenched with saturated aqueous Na+/K+-tartrate solution (10 mL). The resulting mixture was vigorously stirred until formation of clear separation of both organic and aqueous phase was observed. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (6 x 3 mL); The combined organic extracts were washed with saturated aqueous NaCl solution (5 mL), dried over anhydrous Na_2SO_4, and the solvents were evaporated. The crude was purified by silica gel column chromatography using (hexanes/EtOAc) to yield alcohol **34** (0.494 g, 85% yield) as a clear oil and the other minor epimer which was not separated earlier was separable at this stage. Major isomer was utilized further. R_f = 0.5 (SiO_2, 20% EtOAc/hexane); $[\alpha]_D^{20}$ = +20.1 (*c* 1.12, $CHCl_3$); IR (neat) 3503, 2945, 1721, 1515, 1463, 1377, 1248, 1047, 946, 831, 757, 670 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.27-7.23 (m, 2H), 6.89-6.85 (m, 2H), 5.02 (dd, *J* = 7.8, 3.3 Hz, 1H), 4.55 (q, *J* = 10.8 Hz, 2H), 4.12 (dd, *J* = 9.3, 3.0 Hz, 1H), 3.88 (m, 1H), 3.80 (s, 3H), 3.54-3.43 (m, 2H), 3.28 (dd, *J* = 7.3, 3.5 Hz, 1H), 2.73 (qd, *J* = 7.2, 3.0, 7.0 Hz, 1H), 2.23-2.16 (m, 1H), 2.11-2.05 (m, 1H), 1.94-1.85 (m, 2H), 1.37-1.30 (m, 2H), 1.21 (d, *J* = 7.1 Hz, 3H), 1.03 (dd, *J* = 6.7, 4.5 Hz, 6H), 0.99 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.92-0.88 (m, 21H), 0.73 (d, *J* = 7.1 Hz, 3H), 0.08 (d, *J* = 4.4 Hz, 6H), 0.05 (d, *J* = 2.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 174.6, 159.0, 131.0, 128.6, 113.6, 84.8, 78.6, 74.0, 73.7, 73.2, 64.4, 55.2, 45.7, 42.7, 37.7, 37.5, 30.6, 25.9, 25.8, 23.3, 21.6, 18.1, 18.0, 16.5, 15.3, 14.7, 10.6, 9.4, 9.1, -4.3, -4.5, -4.6; ESI-HRMS: Calcd *m/z*, For $C_{39}H_{74}O_7NaSi_2$ $(M+Na)^+$: 733.4871, found 733.4869.

(2*R*,3*R*,4*R*,5*R*)-(3*S*,4*S*,5*S*,6*S*)-3-((4-Methoxybenzyl)oxy)-2,4,6-trimethyl-7-oxononan-5-yl 3,5-bis((*tert*-butyldimethylsilyl)oxy)-2,4-dimethylheptanoate (35)

To a solution of IBX (0.315 g, 1.12 mmol) in DMSO (1.0 mL) was added compound **34** (400 mg, 0.56 mmol) dissolved in CH_2Cl_2 (2 mL). The reaction mixture was stirred at rt. for 2 h and quenched by the addition of aqueous saturated $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the organic layer washed with aqueous saturated $NaHCO_3$ (9 x 1 mL) solution, water (4 x 1 mL), brine (8 x 1 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was used directly for further step.

To the solution of above crude aldehyde in THF (10 mL) at 0 ºC was added EtMgBr (1.68 mL, 1.68 mmol, 1 M in THF) drop wise. The solution was then allowed to warm up to rt over 1 h. The reaction was quenched with saturated aq NH_4Cl (10 x 1mL) and extracted with EtOAc (6 x 3 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude material which was passed through a small pad of silica gel to afford the mixture of secondary alcohols as a colorless oil. The mixture was directly utilized for oxidation reaction with IBX.

To the solution of IBX (0.398 g, 1.42 mmol) in DMSO (1.0 mL) was added above crude mixture of alcohols in CH_2Cl_2 (2 mL). The reaction mixture was stirred at rt. for 2 h and quenched by the addition of aq saturated $Na_2S_2O_3$ solution. The aq layer was extracted with CH_2Cl_2 and the organic layer washed with saturated $NaHCO_3$ solution (10 x 1mL), water (5 x 1 mL), brine (9 x 1 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by silica gel column chromatography (hexane/EtOAc) to yield ketone **35** (0.251 g, 77% yield) as a clear oil. R_f = 0.5 (SiO_2, 20% EtOAc/hexane); $[\alpha]_D^{20}$ = +44.3 (*c* 1.45, $CHCl_3$); IR(neat): 2952, 2932, 2857, 1732, 1613, 1514, 1464, 1382, 1301, 1251, 1186, 1065, 1032, 941, 833, 755, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.32-7.27 (m, 2H), 6.91-6.86 (m, 2H), 5.35 (dd, *J* = 7.4, 4.1 Hz, 1H), 4.58 (q, *J* = 10.9 Hz, 2H), 4.12 (dd, *J* = 9.8, 2.9, Hz,

1H), 3.90-3.84 (m, 1H), 3.81 (s, 3H), 3.22 (dd, *J* = 7.2, 4.0 Hz, 1H), 3.11-3.02 (m, 1H), 2.59 (qd, *J* = 7.1, 3.0, 7.0 Hz, 1H), 2.50-2.39 (m, 1H), 2.36-2.34 (m, 1H), 2.20-2.11 (m, 1H), 1.93-1.81 (m, 2H), 1.40-1.29 (m, 2H), 1.16 (d, *J* = 7.1 Hz, 3H), 1.04 (dd, *J* = 10.2, 7.2 Hz, 6H), 0.98-0.93 (m, 6H), 0.91 (d, *J* = 3.7 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.69 (d, *J* = 7.1 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (d, *J* = 1.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 212.4, 173.0, 158.9, 131.0, 128.6, 113.7, 85.2, 77.6, 77.2, 73.7, 73.1, 55.2, 48.7, 45.8, 42.7, 37.0, 34.3, 30.7, 25.9, 25.7, 23.2, 20.9, 18.0, 17.9, 16.8, 14.7, 13.7, 10.8, 8.8, 8.7, 7.5, -4.3, -4.4, -4.5, -4.6; ESI-HRMS: Calcd *m/z*, For $C_{41}H_{76}O_7NaSi_2$ $(M+Na)^+$: 759.5027, found 759.5023.

(2*R*,3*R*,4*R*,5*R*)-(3*S*,4*S*,5*S*,6*S*)-3-((4-Methoxybenzyl)oxy)-2,4,6-trimethyl-7-oxononan-5-yl 3,5-dihydroxy-2,4-dimethylheptanoate (36)

To a cooled (0 °C) solution of compound **35** (200 mg, 0.27 mmol) in THF (9 mL) in a Teflon tube was added HF-Pyridine (0.2 mL). The reaction mixture was stirred 1 h at 0 °C and 6 h at rt. Reaction mixture was quenched with saturated $NaHCO_3$ solution (6 mL) and the aqueous layer was extracted with EtOAc (5 x 3 mL) and washed with brine (1 x 5 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by column chromatography (hexanes/EtOAc) to yield diol **36** (104 mg, 76% yield) as a clear oil R_f = 0.5 (SiO_2, 40% EtOAc/hexane); $[\alpha]_D^{20}$ = +34.3 (*c* 0.9, $CHCl_3$); IR(neat): 3456, 2956, 2925, 1717, 1607, 1516, 1458, 1378, 1252, 1172, 1073, 1025, 801, 755, 671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.31-7.24 (m, 2H), 6.92-6.85 (m, 2H), 5.28 (dd, *J* = 6.8, 4.4 Hz, 1H), 4.55 (dd, *J* = 13.4, 10.8 Hz, 2H), 3.81 (s, 3H), 3.64 (td, *J* = 7.8, 2.9 Hz, 1H), 3.50 (dd, *J* = 8.3, 3.9 Hz, 1H), 3.18-3.08 (m, 2H), 2.83 (qd, *J* = 7.1, 3.1 Hz, 1H), 2.45-2.32 (m, 1H), 2.32-2.21 (m, 1H), 2.19-2.09 (m, 1H), 1.92-1.81 (m, 1H), 1.72-1.65 (m, 1H), 1.64-1.58 (m, 1H), 1.42 (dt, *J* = 7.4, 7.1 Hz, 1H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H) 0.98-0.90 (m, 12H), 0.87 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 213.2, 175.1, 159.1, 130.8, 129.0, 113.7, 85.9, 79.0, 77.7, 76.6, 74.2, 55.2, 47.8, 42.7, 41.6, 36.9, 35.0, 31.0, 27.1, 20.8, 17.3, 15.4, 15.3, 14.3, 14.1, 9.4, 7.5; ESI-HRMS: Calcd *m/z* For $C_{29}H_{48}O_7$: 531.3298, found 531.3296.

(2*R*,3*R*,4*S*)-(3*S*,4*S*,5*S*,6*S*)-3-((4-Methoxybenzyl)oxy)-2,4,6-trimethyl-7-oxononan-5-yl 3-hydroxy-2,4-dimethyl-5-oxoheptanoate (37)

Dess-Martin periodinane (30 mg, 0.070 mmol, 1.8 equiv.) was added to a stirred solution of the diol **36** (20 mg, 0.039 mmol) and $NaHCO_3$ (39 mg, 0.47 mmol, 12 equiv.) in CH_2Cl_2 (4 mL). After stirring for 1 h, the mixture was diluted with pentane, filtered through a thin SiO_2 plug and concentrated under reduced pressure to give a crude material which was purified by column chromatography over silica gel (hexanes/EtOAc) to afford **37** (12.5 mg, 63 %). R_f = 0.5 (SiO_2, 20% EtOAc/hexane); $[\alpha]_D^{20}$ = +34.2 (*c* 0.33, $CHCl_3$), (Lit.[6b] $[\alpha]_D$ = +30.0 (*c* 0.25, $CHCl_3$); IR(neat): 3499, 2970, 1712, 1610, 1514, 1458, 1374, 1244, 1173, 1073, 973, 819, 753, 666 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): *δ* 7.37-7.31 (m, 2H), 6.86-6.81 (m, 2H), 5.45 (dd, *J* = 7.4, 4.4 Hz, 1H), 4.62 (d, *J* = 10.8 Hz, 1H), 4.51 (d, *J* = 10.7 Hz, 1H), 3.81-3.75 (m, 1H), 3.69 (d, *J* = 8.5 Hz, 1H), 3.31 (s, 3H), 3.18 (dd, *J* = 6.8, 4.1 Hz, 1H), 3.10 (m, 1H), 2.70-2.62 (m, 2H), 2.25-2.11 (m, 4H), 1.87-1.79 (m, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.01-0.98 (m, 6H), 0.98-0.93 (m, 9H), 0.91 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): *δ* 214.2, 212.0, 174.1, 159.7, 131.4, 129.4, 114.1, 85.9, 77.9, 76.6, 74.4, 54.7, 48.8, 48.7, 43.9, 37.1, 36.0, 34.6, 31.2, 21.3, 17.2, 15.8, 15.0, 14.5, 14.0, 7.7, 7.6; ESI-HRMS: Calcd *m/z*, For $C_{29}H_{46}O_7$ Na $(M+Na)^+$: 529.3141, found 529.3131.

(2*R*,3*R*,4*S*)-(2*R*,3*S*,4*S*,5*S*,6*S*)-2-Ethyl-2-hydroxy-6-isopropyl-3,5-dimethyltetrahydro-2H-pyran-4-yl 3-hydroxy-2,4-dimethyl-5-oxoheptanoate (1) (Dolabriferol)

DDQ (9.69 mg, 0.042 mmol) was added to the PMB ether **37** (12 mg, 0.023 mmol), in CH_2Cl_2 (2 mL) and P^H =7 buffer (0.2 mL) at 0 °C. The mixture was stirred for 1 h, then diluted with P^H =7 buffer solution (2 mL) and CH_2Cl_2 (2 mL). The organic phase was separated, the aqueous phase was extracted with CH_2Cl_2 (2 × 2 mL) and the combined organic extracts was dried over Na_2SO_4, then concentrated under reduced pressure to give the crude material which was further purified by column chromatography over silica gel (hexanes/EtOAc) (8:2) to afford the (-)-dolabriferol **1** as a white solid (4.5 mg, 50 %). R_f = 0.4 (SiO_2, 20% EtOAc/hexanes); m.p 115-118, $[\alpha]_D^{25}$ = −28.3 (*c* 0.3, $CHCl_3$) (Lit.[2] $[\alpha]_D^{25}$ = −29.4 (*c* 0.7, $CHCl_3$); IR (neat): 3433, 2962, 2923, 2854, 1718, 1460, 1378, 1275, 1240, 1165, 1127, 1090, 978, 912, 840, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 5.25 (t, *J* = 2.6 Hz, 1H), 3.79-3.73 (m, 1H), 3.65 (bs, 1H), 3.61 (dd, *J* = 10.6, 2.1 Hz, 1H), 3.46 (bs, 1H), 2.79 (dq, 7.1, 7.1 Hz, 1H), 2.74 (dq, 7.1, 4.8 Hz, 1H), 2.57 (dq, *J* = 14.4, 7.3 Hz, 1H), 2.46 (dq, *J* = 14.4, 7.3 Hz, 1H), 1.91 (dq, *J* = 7.2, 2.8 Hz, 1H), 1.81 (dqq, *J* = 2.0, 6.8, 6.8 Hz, 1H), 1.79-1.73 (m, 1H), 1.68-1.59 (m, 2H), 1.33 (d, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.8, Hz, 3H), 1.00 (d, *J* = 7.2, Hz, 3H) 0.91 (t, *J* = 7.4 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 215.1, 173.7, 98.5, 76.8, 75.6, 72.5, 49.4, 43.6, 39.4, 36.4, 35.9, 32.4, 27.9, 20.2, 15.5, 14.3, 13.9, 12.9, 12.7, 7.4, 7.2; ESI-HRMS Calcd *m/z*, for $C_{21}H_{38}O_6Na$ $(M+Na)^+$: 409.2566, Found: 409.2564.

Acknowledgements

GN acknowledges UGC, New Delhi for financial assistance. BS acknowledge CSIR, New Delhi for financial assistance and PS acknowledge DST and CSIR, New Delhi for funding the project under budget head GAP-584.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: polyketide • aldol • natural products • Yamaguchi esterification• Sharpless epoxidation

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10.1002/ejoc.201701748

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FULL PAPER

Total Synthesis

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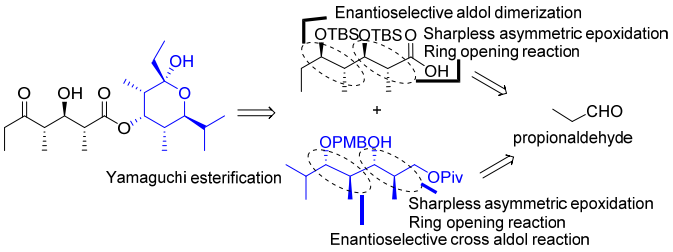
Page No. – Page No.
Title: Stereoselective total synthesis of non-contiguous polyketide natural product (-)-dolabriferol



The stereoselective total synthesis of dolabriferol is accomplished in 17 steps following a divergent cum convergent approach. The effect of protecting groups on alcohol substrate played a pivotal role for Yamaguchi esterification reaction