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Synthesis of (4*R*,6*S*,7*R*)-7-hydroxy-4,6-dimethyl-3-nonanone and (3*R*,5*S*,6*R*)-6-hydroxy-3,5-dimethyl-2-octanone

Gowravaram Sabitha [a,*], Chitti Srinivas [a], Chittapragada Maruthi [a], Jhillu Singh Yadav [a,b]

[a] *Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500007, India*
[b] *Bee Research Chair, College of Food and Agriculture Science, King Saud University, Riyadh, Saudi Arabia*

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ABSTRACT

The synthesis of (4*R*,6*S*,7*R*)-7-hydroxy-4,6-dimethyl-3-nonanone and (3*R*,5*S*,6*R*)-6-hydroxy-3,5-dimethyl-2-octanone is described as their acetates using a desymmetrization strategy as well as an Evans *syn* aldol strategy.

1. Introduction

The potential economic and environmental importance of biological pest control is an undergoing experimental evaluation, and the successful use of natural insect attractants has been reported by several groups. Insect attractants have been used to reduce pest populations by employing attractant-baited traps. The relatively small amounts of synthetic attractants required, minimizes the possibility of environmental pollution, and the species specificity of many natural attractants reduces the risk of destroying beneficial insects such as predators, parasites, and pollinators resistant to natural attractants is very unlikely. Thus the presence of a synthetic approach has been very important in pheromone research.

(3*S*,11*S*)-Dimethylnonacosan-2-one (produced by females of the German cockroach, *Blattella germanica*),[1] (4*S*)-methyl-3-heptanone (the principal alarm pheromone of the leaf-cutting ant, *Atta texana*),[2] (*Z*)-(14*R*)-methyl-8-hexadecen-1-ol (the dermestid beetle pheromone artifact),[3] serricornin (an insect derived sex pheromone), are a few examples of pheromones that attracted the interest of synthetic chemists (Fig. 1).

Serricornin and its isomers are insect derived sex pheromones, more effective as traps for the beetles *Stegobium panecium* and *Lasioderma serricorne*. Francke and his co-workers have identified stereoisomers of nor-serricornin (a stereoisomer of serricornin) as the pheromone components of the bostrychid beetle, *Dinoderus bifoveolatus*.

The structures were established as (4*R*,6*S*,7*R*)-**1** and (3*R*,5*S*,6*R*)-**2** as well as their stereoisomers (4*R*,6*S*,7*S*)-**1′** and (3*R*,5*S*,6*S*)-**2′** by means of gas chromatography of their acetates **3**, **4**, **3′**, and **4′** (Fig. 2).

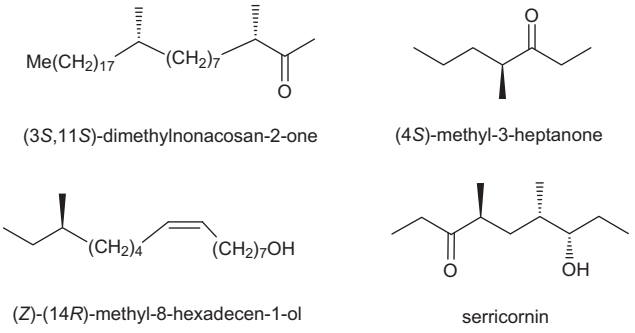

Figure 1. Examples of pheromones.

The only total synthesis of these stereoisomers was reported by Mori et al.[4] Starting from *meso*-2,4-dimethylglutaric anhydride. Therefore, the synthesis of these isomers attracted our attention. In a continuation of our interest in the exploitation of desymmetrization strategies for the synthesis of various natural products,[5] we herein report the synthesis of (4*R*,6*S*,7*R*)-7-hydroxy-4,6-dimethyl-3-nonanone **1** and (3*R*,5*S*,6*R*)-6-hydroxy-3,5-dimethyl-2-octanone **2** and their respective isomers **1′**, **2′** as their acetates **3**, **4**, **3′**, **4′**, respectively. The compounds were also synthesized in another route exploiting an Evans-aldol reaction.

2. Results and discussion

The intermediate **5** with three stereogenic centers was envisaged as a common intermediate for the synthesis of **3**, **4**, **3′**, **4′** as represented in the retrosynthetic analysis shown below (Scheme 1) and could be made by two different strategies. In route **a**, the desymmetrization of bicyclic olefin **8** was used, whereas in route

* Corresponding author. Tel.: +91 40 27191629; fax: +91 40 27160512.
E-mail address: gowravaramsr@yahoo.com (G. Sabitha).

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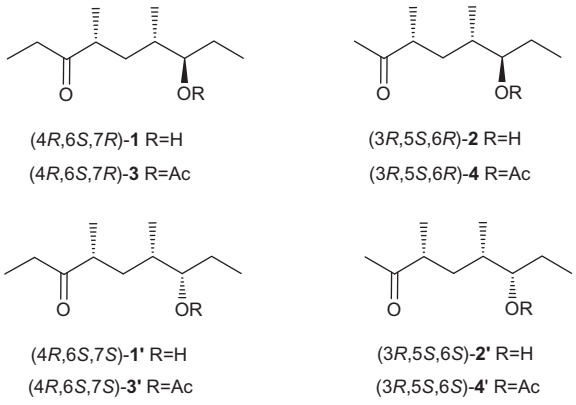


Figure 2. Structures of the pheromone components of a Bostrchid beetle (**1** and **2**), and their stereoisomers (**1′** and **2′**).

b, an Evans *syn* aldol reaction was utilized. Subsequent Grignard and oxidation reactions as well as Mitsunobu inversion provided the respective target molecules.

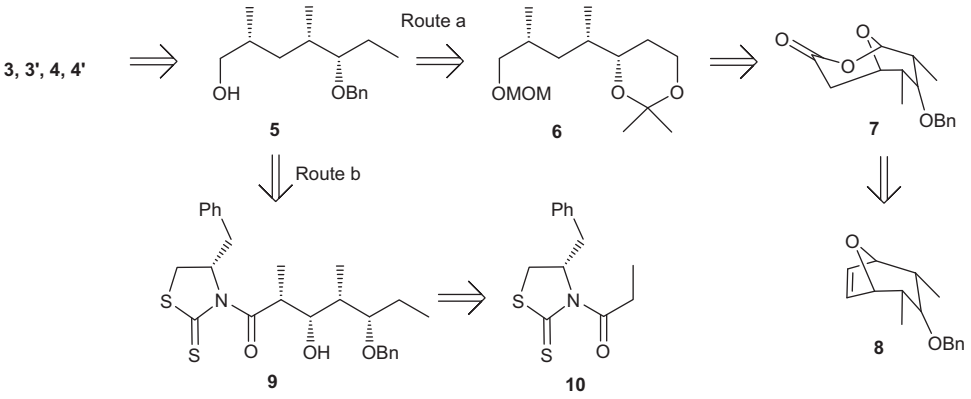
The synthesis of (4*R*,6*S*,7*R*)-7-hydroxy-4,6-dimethyl-3-nonanone **1** and (3*R*,5*S*,6*R*)-6-hydroxy-3,5-dimethyl-2-octanone **2** started from the known bicyclic lactone **7**,[5e] which was prepared using a desymmetrization strategy. The key fragment **5**, which contains all the required stereocenters of target molecules **3**, **3′**, **4**, **4′**, was prepared on the basis of the desymmetrization of bicyclic olefin **8** using Brown's chiral hydroboration with diisopropylcamphenylborane [(+) Ipc_2BH]. A high enantiomeric purity (97% ee) was achieved in the hydroboration of **8** using (+)-Ipc_2BH prepared from borane-dimethyl sulfide complex and an excess of (−)-α-pinene (Scheme 2). The chiral bicyclic alcohol **11** was converted into the bicyclic lactone **7** by following a standard procedure.[5e] Next, attention was directed to the opening of lactone **7**. Thus, the opening of bicyclic lactone **7** with LAH yielded triol **12** in a 90% yield. The chemoselective protection of the 1,3-diol using 2,2-DMP, *p*TSA (catalytic) in CH_2Cl_2 afforded the corresponding acetonide **13** in an 89% yield, which was confirmed by ^{13}C NMR spectrum analysis (δ = 98.0 ppm for the acetonide carbon flanked by two oxygen atoms). After protection of the primary hydroxyl group as MOM ether[6] **14** using MOMCl and DIPEA, debenzylation of **14** under Birch conditions[7] with Li/liq NH_3 in THF gave alcohol **15** in a 91% yield. The C-3 oxygen of compound **15** needs to be deoxygenated to gain the complete stereochemistry of the target molecules. Accordingly, compound **15** was converted into xanthate ester **16** using NaH, carbon disulfide and methyl iodide. The ^1H NMR spectrum of xanthate ester **16** showed a characteristic signal as a dd (doublet of doublets) at δ = 5.90 ppm for the methine proton attached to xanthate group, a singlet at δ = 2.56 ppm for methyl protons attached to sulfur in the xanthate group. Then it was deoxygenated by tri-*n*-butyltin hydride in the presence of a catalytic amount of AIBN as a radical initiator (Barton–McCombie deoxygenation)[8] to afford compound **6** in an 88% yield, which was confirmed by ^1H NMR analysis. ^1H NMR of the **6** showed the absence of proton resonance at δ = 5.90 ppm corresponding to the methane attached to the xanthate group.

The acetonide group within **6** was hydrolyzed using a catalytic amount of PPTS in MeOH to yield diol **17**. The primary hydroxyl group in compound **17** was selectively tosylated with TsCl, Et_3N, and a catalytic amount of $^nBu_2SnO$ in CH_2Cl_2 to furnish monotosylate **18** in a 95% yield,[9] followed by reductive cleavage of the sulfonate with LAH, in THF to form **19** in an 88% yield. Next, the secondary hydroxyl group was protected as benzyl ether **20** using NaH and BnBr in THF. Then the primary MOM group was deprotected by using a catalytic amount of *p*TSA in MeOH to yield the primary alcohol **5** in an 87% yield.

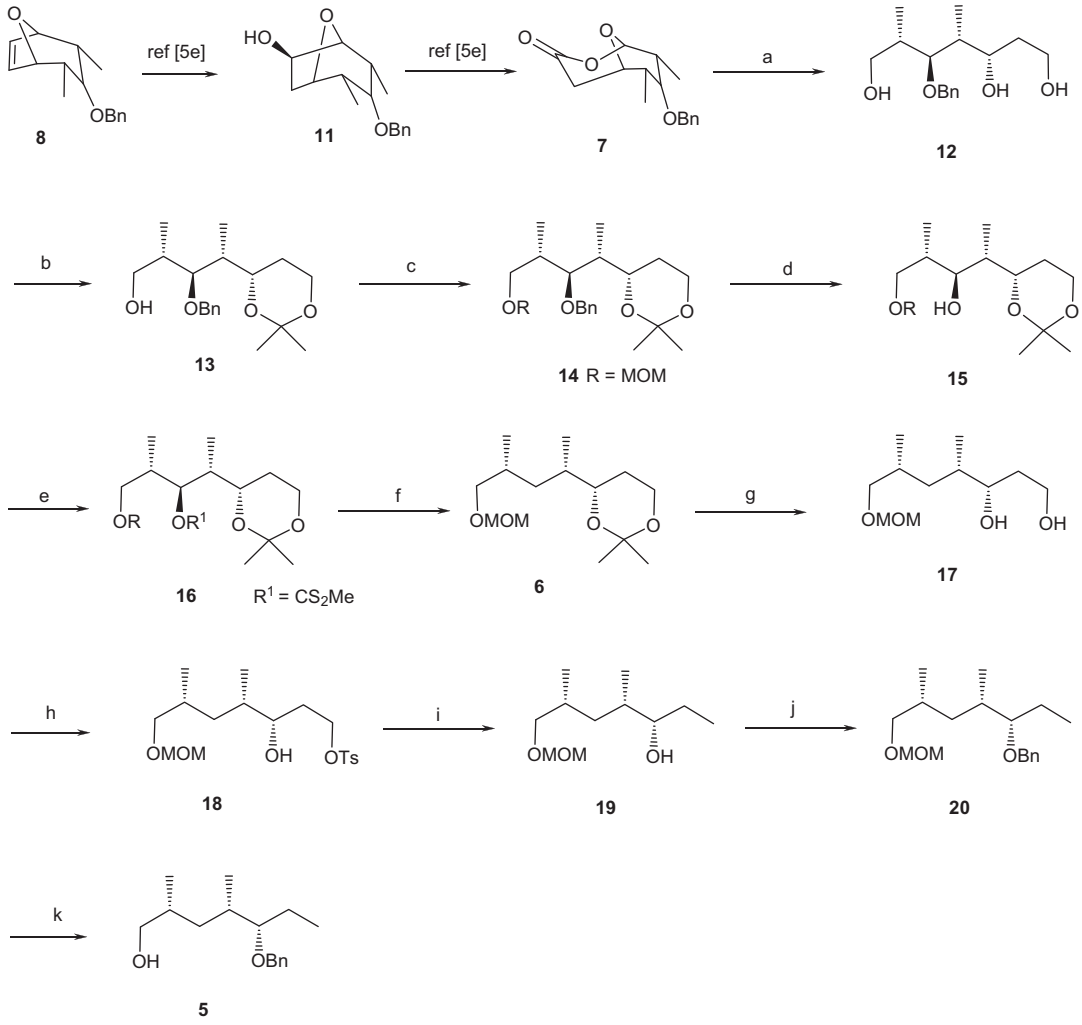
Intermediate **5** was also prepared by another route employing an Evans *syn* aldol reaction (Scheme 3). Accordingly propanal was subjected to 'Evans *syn* aldol' reaction conditions[10] employing an enolate of thiazolidinethione **10**, affording aldol adduct **21** in an 85% yield after column chromatography. Reductive cleavage of the chiral axiliary using $NaBH_4$, afforded diol **22**. The diol **22** was treated with benzaldehyde dimethyl acetal to yield benzylidine acetal **23** in a 91% yield. Regioselective reductive acetal cleavage at the less hindered oxygen with DIBAL-H[11] at −15 °C afforded the primary alcohol **24** in a 90% yield. Oxidation of primary alcohol **24** using IBX in DMSO/CH_2Cl_2 gave aldehyde **25**. Aldehyde **25** was again subjected to an Evans *syn* aldol reaction with thiazolidinethione **10**. Thus, two aldol reactions allowed the incorporation of four stereocenters. Reductive cleavage of the chiral axiliary **9** using $NaBH_4$, afforded diol **26**. Silylation of the primary alcohol provided TBDMS ether **27** in a 95% yield. The free hydroxyl group was converted into the xanthate ester **28** using NaH, carbon disulfide, and methyl iodide, and deoxygenated by using tri-*n*-butyltin hydride in the presence of a catalytic amount of AIBN as a radical initiator (Barton–McCombie deoxygenation)[8] to afford compound **29** in an 87% yield. Removal of the silyl group provided compound **5**, which was identical in all respects with the alcohol **5** prepared in Scheme 2.

The intermediate **5** prepared by these two routes was utilized for the preparation of target molecules. Oxidation of compound **5** using IBX in DMSO/DCM gave aldehyde **30** (Scheme 4). Grignard reaction of aldehyde **30** with EtMgBr in dry THF gave a secondary alcohol, which without isolation was converted into a keto compound **31**.

Removal of the benzyl group afforded hydroxyl product **1′**. The ^1H NMR spectrum of debenzylated product **1′** was found to be complicated due to a mixture of open and hemi-acetal tautomers and thus was used directly for acetylation. Therefore **1′** was immediately



Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) LAH, dry THF, reflux, 4 h, 90%; (b) 2,2 DMP, *p*TSA, dry CH_2Cl_2, 0 °C to rt, 3 h, 89%; (c) MOMCl, *i*-Pr_2NEt, dry CH_2Cl_2, 0 °C to rt, 4 h, 90%; (d) Li, liq NH_3, THF, 10 min, 91%; (e) NaH, CS_2, MeI, dry THF, 0 °C to rt, 5 h, 92%; (f) $^nBu_3SnH$, AIBN, toluene, reflux, 2 h, 88%; (g) PPTS, MeOH, 0 °C to rt, 3 h, 85%; (h) *p*-TsCl, $^nBu_2SnO$, Et_3N, dry CH_2Cl_2, 0 °C to rt, 4 h, 95%; (i) LAH, dry THF, reflux 3 h, 88%; (j) NaH, BnBr, dry THF, 0 °C to rt 5 h, 90%; (k) PTSA, MeOH, 0 °C to rt, 6 h, 87%.

converted into its acetate by treating with acetic anhydride, triethylamine, and a catalytic amount of DMAP to afford the final product **3′**. Mitsunobu inversion[12] of hydroxy compound **1′** at C-7 using TPP, DEAD in the presence of AcOH directly gave final product **3**.

Similarly, Grignard reaction of aldehyde **30** with MeMgBr in dry Ether gave a secondary alcohol, which without isolation was converted into a keto compound **32**. Removal of the benzyl group afforded hydroxy product **2′**, which by following the above procedure was converted into final products **4′** and **4**.

3. Conclusion

In summary, the versatility of a desymmetrization strategy and chlorotitanium mediated asymmetric aldol reactions was demonstrated in a higly stereoselective fashion for the synthesis of various stereoisomers of serricornin.

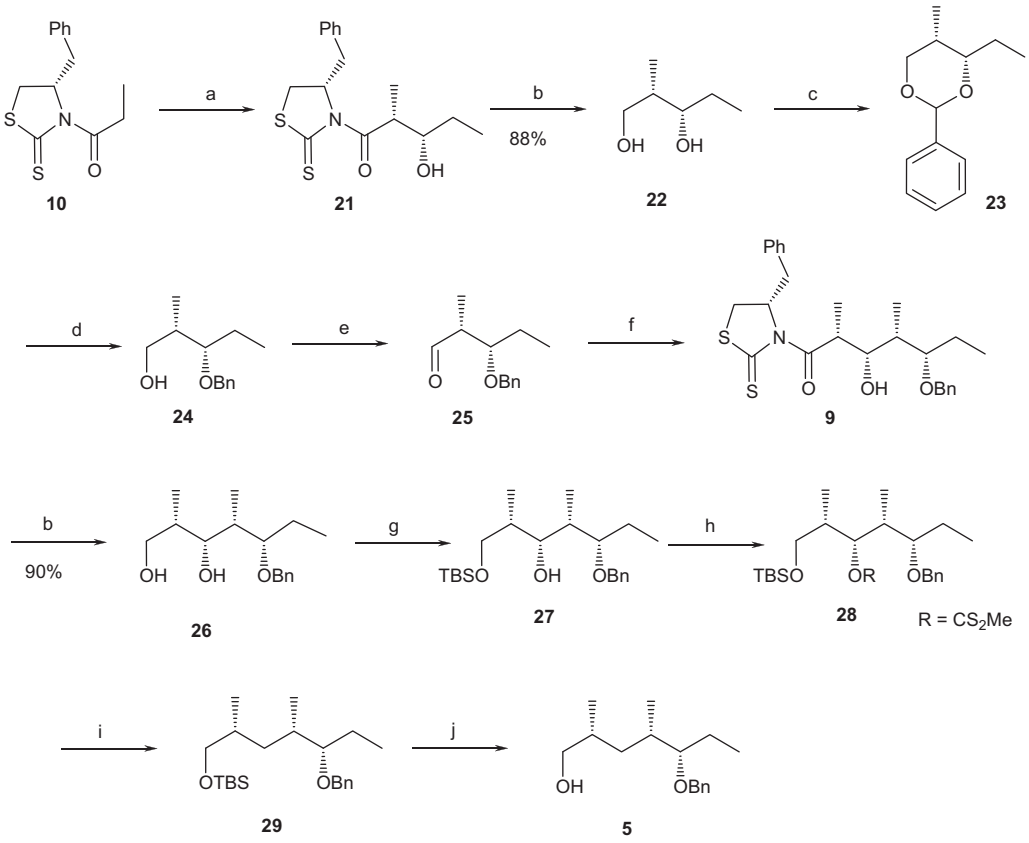
4. Experimental

4.1. General

Reactions were conducted under N_2 in anhydrous solvents such as CH_2Cl_2, THF, Benzene, Toluene, DMSO, and MeOH. All reactions were monitored by TLC (silica-coated plates and visualizing under UV light). Light petroleum ether (bp 60–80 °C) was used. Yields refer to chromatographically and spectroscopically (^1H, ^{13}C NMR) homogeneous materials. Air-sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator. ^1H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) spectrometers. Chemical shifts (δ) are reported relative to TMS ($\delta = 0.0$) as an internal standard. Mass spectra were recorded in E1 conditions at 70 eV on an LC–MSD (Agilent technologies) spectrometers. All high resolution spectra were recorded on QSTAR XL hybrid ms/ms system (Applied Bio systems/MDS sciex, foster city, USA), equipped with an ESI source (IICT, Hyderabad). Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. Optical rotations were measured with JASCO DIP-370 Polarimeter at 25 °C.

4.1.1. (3*S*,4*R*,5*S*,6*S*)-5-(Benzyloxy)-4,6-dimethylheptane-1,3,7-triol 12

To a stirred suspension of $LiAlH_4$ (0.541 g, 14.23 mmol) in dry THF (30 mL) at 0 °C, a solution of lactone **7** (2.62 g, 9.49 mmol) in dry THF (20 mL) was added dropwise. The reaction mixture was refluxed for 4 h and cooled to 0 °C, diluted with ether and quenched



Scheme 3. Reagents and conditions: (a) $TiCl_4$, *i*-Pr_2NEt, propanal, dry CH_2Cl_2, 1 h, 85%; (b) $NaBH_4$, MeOH, 0 °C to rt, 1 h, 88%; (c) Ph–$CH(OMe)_2$, PPTS, dry CH_2Cl_2, 0 °C to rt, 2 h, 91%; (d) DIBAL-H, dry CH_2Cl_2, −15 °C 1 h, 90%. (e) IBX, DMSO, dry CH_2Cl_2, 0 °C to rt, 2 h, 88% (f) $TiCl_4$, *i*-Pr_2NEt, **10**, dry CH_2Cl_2, 1 h, 80%; (g) TBDPS-Cl, imidazole, CH_2Cl_2, 0 °C to rt, 2 h, 95%; (h) NaH, CS_2, MeI, 0 °C to rt, dry THF 0 °C to rt, 5 h, 91%; (i) $^nBu_3SnH$, AIBN, Toluene, reflux, 2 h, 87%; (j) PTSA, MeOH, 0 °C to rt, 30 min, 93%.

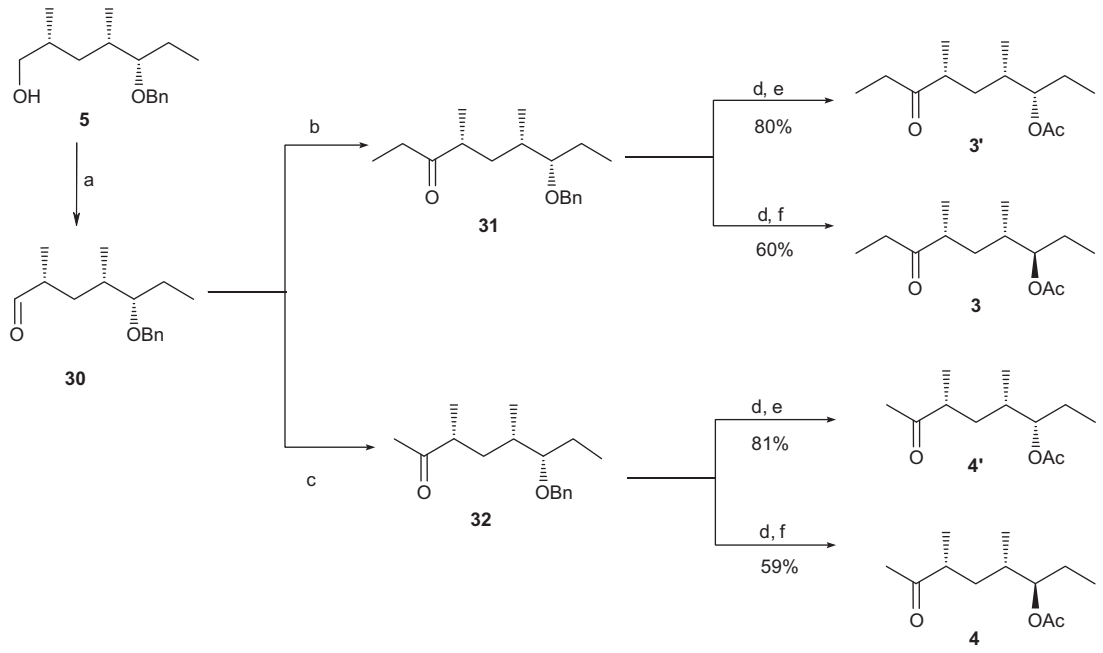
with dropwise addition of saturated aqueous Na_2SO_4. The solid material was filtered and washed thoroughly with hot ethyl acetate several times. The combined organic layers were dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 8:2) to afford the pure compound **12** (2.41 g, 90%) as a viscous liquid. $[\alpha]_D^{25} = -6.9$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3397, 2931, 1637, 1457, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38–7.27 (m, 5H), 4.67 (s, 2H), 4.22 (d, *J* = 10.6 Hz, 1H), 3.82–3.72 (m, 3H), 3.64 (dt, *J* = 14.3, 3.8 Hz, 1H), 3.49 (dd, *J* = 7.6, 3.8 Hz, 1H), 3.37–3.31 (br s, OH, 1H), 2.56–2.46 (br s, OH, 1H), 2.10–1.98 (m, 1H), 1.94–1.79 (m, 2H), 1.75–1.66 (m, 1H), 1.45–1.34 (m, 1H), 1.11 (d, *J* = 7.5 Hz, 3H), 1.01 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.0, 129.0, 128.5, 128.3, 88.6, 77.8, 70.9, 64.4, 62.2, 39.6, 38.2, 37.0, 15.4, 12.2; ESI: *m*/*z* = 305 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{16}H_{26}O_4Na$: 305.1728, found: 305.1738.

4.1.2. (2*S*,3*S*,4*R*)-3-(Benzyloxy)-4-((*S*)-2,2-dimethyl-1,3-dioxan-4-yl)-2-methylpentan-1-ol 13

To a solution of triol **12** (2.35 g, 8.32 mmol) in dry CH_2Cl_2 (30 mL), 2,2-dimeothoxypropane (2.04 mL, 16.64 mmol) and *p*TSA (0.16 g, 0.83 mmol) were added. The mixture was stirred at ambient temperature for 3 h. After completion of the reaction solid $NaHCO_3$ was added to neutralize the *p*TSA and filtered. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 2:8) to afford the pure monoacetonide **13** (2.38 g, 89%) as a white solid. $[\alpha]_D^{25} = +22.5$ (*c* 1.5, $CHCl_3$); IR (neat): ν_{max} 3419, 2925, 1640, 1456, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.22 (m, 5H), 4.63 (ABq, *J* = 11.3, 3.0 Hz, 2H), 4.25 (dt, *J* = 12.1, 2.7 Hz, 1H), 3.92 (dt, *J* = 12.1 2.7 Hz, 1H), 3.80 (dd, *J* = 11.3, 3.8 Hz, 2H), 3.53 (dd, *J* = 11.3, 4.5 Hz, 1H), 3.44 (dd, *J* = 9.1, 3.0 Hz, 1H), 2.64 (br s, OH, 1H), 1.96–1.69 (m, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.27–1.15 (m, 1H), 1.17 (d, *J* = 7.6 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.2, 128.5, 127.7, 127.2, 98.0, 85.6, 75.2, 67.4, 64.4, 60.0, 41.4, 36.3, 30.0, 28.6, 19.6, 16.3, 10.4; ESI: *m*/*z* = 345 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{19}H_{30}O_4Na$: 345.2041, found: 345.2035.

4.1.3. (*S*)-4-((2*R*,3*S*,4*S*)-3-(Benzyloxy)-5-(methoxymethoxy)-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxane 14

To a stirred solution of alcohol **13** (2.3 g, 7.13 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C under N_2, $^iPr_2NEt$ (2.43 mL, 14.26 mmol) was added followed by dropwise addition of MOMCl (0.85 mL, 10.70 mmol). After the reaction was complete, the reaction mixture was quenched by adding a saturated solution of $NaHCO_3$ and the product was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. The residue was concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to afford the pure compound **14** (2.35 g, 90%) as a clear colorless liquid. $[\alpha]_D^{25} = -2.0$ (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 3445, 2931, 2880, 1633, 1451, 1377, 1100, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.33–7.20 (m, 5H), 4.60 (ABq, *J* = 11.3, 3.8 Hz, 2H), 4.55 (s, 2H), 4.22 (dt, *J* = 11.3, 2.3 Hz, 1H), 3.90 (dt, *J* = 12.1, 2.3 Hz, 1H), 3.79 (ddd, *J* = 11.3, 5.3, 1.5 Hz, 2H), 3.67 (dd, *J* = 9.8, 4.5 Hz, 1H), 3.35 (dd, *J* = 12.8, 3.0 Hz, 1H), 3.32 (s, 3H), 2.13–2.01 (m, 1H), 1.91–1.78 (m, 1H), 1.74–1.64 (m, 1H), 1.37 (s, 3H), 1.33 (s, 3H), 1.25–1.13 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$,



Scheme 4. Reagents and conditions: (a) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 2 h, 89%; (b) (i) Mg, EtBr, dry THF, 0 °C to rt, 2 h, 90%; (ii) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 2 h, 92%; (c) (i) Mg, MeI, dry Ether, 0 °C to rt, 2 h, 88%; (ii) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 2 h, 90%; (d) 10% Pd/C, Benzene, rt, 4 h, (e) Et_3N, Ac_2O, DMAP, CH_2Cl_2, 0 °C to rt, 2 h; (f) TPP, AcOH, DEAD, dry THF, 0 °C to rt, 1 h.

75 MHz): δ 139.2, 128.3, 127.3, 126.8, 98.0, 96.4, 83.2, 74.7, 69.1, 67.5, 60.0, 55.0, 41.2, 36.1, 30.2, 28.8, 19.7, 16.7, 10.8; ESI: *m*/*z* = 389 $[M+Na]^+$.

4.1.4. (2*S*,3*S*,4*S*)-4-((*S*)-2,2-Dimethyl-1,3-dioxan-4-yl)-1-(methoxymethoxy)-2-methylpentan-3-ol 15

To a freshly distilled ammonia (30 mL) in 100 mL two neck roundbottomed flask fitted with a cold finger condenser, was added lithium metal (0.44 g, 62.75 mmol) in fractions at −33 °C and the resulting gray colored suspension was stirred for 30 min. To this was added compound **14** (2.3 g, 6.27 mmol) in dry THF (20 mL). The reaction mixture was then stirred for another 10 min at −33 °C and quenched by the addition of solid NH_4Cl and then the excess ammonia was allowed to evaporate. The residue left was partitioned between water and ether and the aqueous phase extracted with ether. The organic layers were combined, washed once with water, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 2:8) to afford the pure compound **15** (1.57 g, 91%) as a clear colorless liquid. $[\alpha]_D^{25} = -20.0$ (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 3496, 2926, 2857, 1732, 1461, 1378, 1244, 1153, 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 4.56 (s, 2H), 4.23 (dt, *J* = 12.1, 3.0 Hz, 1H), 3.95 (dt, *J* = 11.3, 2.7 Hz, 1H), 3.84 (ddd, *J* = 12.1, 5.3, 1.5 Hz, 1H), 3.66 (dd, *J* = 9.8, 4.5 Hz, 1H), 3.51 (dd, *J* = 9.8, 6.8 Hz, 1H), 3.40 (q, *J* = 12.1, 6.1, 1.5 Hz, 1H), 3.34 (s, 3H), 3.26 (d, *J* = 6.8 Hz, 1H), 2.00–1.73 (m, 3H), 1.45 (s, 3H), 1.35 (s, 3H), 1.29–1.17 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 98.5, 96.6, 76.8, 70.8, 69.7, 60.1, 55.2, 38.4, 36.5, 29.8, 26.8, 19.1, 15.3, 11.9; ESI: *m*/*z* = 299 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{14}H_{28}O_5Na$: 299.1834, found: 299.1843.

4.1.5. *O*-(2*S*,3*S*,4*R*)-4-((*S*)-2,2-Dimethyl-1,3-dioxan-4-yl)-1-(methoxymethoxy)-2-methylpentan-3-yl *S*-methyl carbonodithioate 16

To a suspension of NaH (0.26 g, 10.85 mmol) in dry THF (20 mL) at 0 °C was added the alcohol **15** (1.5 g, 5.42 mmol) in dry THF (20 mL) using a syringe under N_2. After stirring the reaction mixture at rt for half an hour, the reaction mixture was cooled to 0 °C and CS_2 (1.3 mL, 21.71 mmol) was added. After stirring for half an hour at 0 °C, MeI (2.70 mL, 43.42 mmol) was added at the same temperature. After completion of the reaction, the reaction mixture was cooled to 0 °C and quenched by addition of satd solution of NH_4Cl, and then the product was extracted with EtOAc. The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to afford the pure compound **16** (1.83 g, 92%) as a clear yellow liquid. $[\alpha]_D^{25} = -9.0$ (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 3450, 2929, 2859, 1736, 1613, 1512, 1459, 1375, 1233, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.90 (dd, *J* = 8.8, 2.9 Hz, 1H), 4.56 (ABq, *J* = 9.5, 6.6 Hz, 2H), 3.91 (td, *J* = 11.7, 2.2 Hz, 1H), 3.84 (dt, *J* = 11.7, 2.2 Hz, 1H), 3.79 (ddd, *J* = 11.7, 5.1, 1.5 Hz, 1H), 3.67 (dd, *J* = 9.5, 4.4 Hz, 1H), 3.33 (s, 3H), 3.29 (dd, *J* = 9.5, 8.1 Hz, 1H), 2.56 (s, 3H), 2.32–2.22 (m, 1H), 2.01–1.92 (m, 1H), 1.90–1.78 (m, 1H), 1.30 (s, 3H), 1.28 (s, 3H), 1.18–1.12 (m, 1H), 1.05 (d, *J* = 7.3 Hz, 3H); 1.00 (d, *J* = 7.3 Hz, 3H); ESI: *m*/*z* = 389 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{16}H_{30}O_5NaS_2$: 389.1432, found: 389.1447.

4.1.6. (*S*)-4-((2*S*,4*R*)-5-(Methoxymethoxy)-4-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxane 6

To a solution of xanthate **16** (1.75 g, 4.77 mmol) in toluene (30 mL), in a two neck 100 mL round bottomed flask equipped with stirring bar and a reflux condenser with a N_2 inlet, was added $(^nBu)_3SnH$ (2.05 mL, 7.64 mmol) followed by a catalytic amount of AIBN (radical initiator). The reaction mixture was refluxed for 2 h. After the reaction was complete, the solvent was evaporated under reduced pressure and the residue was directly purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to furnish pure compound **6** (1.09 g, 88%) as a clear colorless liquid. $[\alpha]_D^{25} = +5.5$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 2928, 2877, 1458, 1378, 1105, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.56 (s, 2H), 3.89 (td, *J* = 11.7, 2.3 Hz, 1H), 3.80 (ddd, *J* = 11.7, 5.4, 1.6 Hz, 1H), 3.60 (ddd, *J* = 11.7, 4.7, 3.3 Hz, 1H), 3.37 (dd, *J* = 9.3, 5.4 Hz, 1H), 3.32

(s, 3H), 3.23 (dd, J = 9.4, 7.0 Hz, 1H), 1.86–1.75 (m, 1H), 1.72–1.44 (m, 5H), 1.39 (s, 6H), 0.95 (d, J = 6.2 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 98.1, 96.5, 72.6, 72.3, 60.1, 55.0, 36.3, 35.3, 30.9, 29.8, 28.2, 19.2, 18.5, 15.3; ESI: m/z = 299 $[M+K]^+$.

4.1.7. (3*S*,4*S*,6*R*)-7-(Methoxymethoxy)-4,6-dimethylheptane-1,3-diol 17

To a stirred solution of compound **6** (1.03 g 3.95 mmol) in MeOH (20 mL) was added a catalytic amount of *p*PTS. The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, $NaHCO_3$ was added to neutralize the *p*PTS and filtered. The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc/pet-ether, 7:3) to afford the pure compound **17** (0.74 g, 85%) as a viscous liquid. $[\alpha]_D^{25} = -4.2$ (c 1.5, $CHCl_3$); IR (neat): ν_{max} 3411, 2928, 1461, 1384, 1109, 1044 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.58 (s, 2H), 3.89–3.74 (m, 3H), 3.33 (s, 3H), 3.36–3.30 (m, 2H), 2.59 (br s, OH, 2H), 1.89–1.68 (m, 2H), 1.67–1.48 (m, 4H), 0.94 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 96.5, 74.3, 73.1, 62.1, 55.1, 37.1, 36.1, 35.4, 30.7, 18.2, 14.6; ESI: m/z = 243 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{11}H_{24}O_4Na$: 243.1572, found: 243.1579.

4.1.8. (3*S*,4*S*,6*R*)-3-Hydroxy-7-(methoxymethoxy)-4,6-dimethylheptyl 4-methylbenzenesulfonate 18

A solution of **17** (0.67 g, 3.04 mmol) in dry CH_2Cl_2 (20 mL), containing Et_3N (0.55 ml, 3.95 mmol), was cooled to 0 °C and treated with *p*-TsCl (0.58 g, 3.04 mmol) and a catalytic amount of $^nBu_2SnO$. The reaction mixture was stirred at room temperature for 4 h, after which it was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:9) to afford the pure compound **18** (1.08 g, 95%) as a light yellow liquid. $[\alpha]_D^{25} = -21.0$ (c 0.5, $CHCl_3$); IR (neat): ν_{max} 3465, 2925, 2855, 1738, 1462, 1368, 1244, 1109, 1044 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, J = 8.0 Hz, 2H) 7.33 (d, J = 8.8 Hz, 2H) 4.56 (s, 2H), 4.27–4.20 (m, 1H), 4.14–4.08 (m, 1H), 3.68–3.62 (m, 1H), 3.33 (s, 3H), 3.31 (d, J = 5. 8 Hz, 2H), 2.47 (s, 3H), 1.94–1.66 (m, 3H), 1.60–1.47 (m, 2H), 1.02–0.94 (m, 1H), 0.93 (d, J = 7.3 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.3, 144.7, 129.8, 127.8, 96.5, 73.0, 70.6, 62.3, 55.1, 37.2, 35.6, 33.4, 30.7, 20.9, 18.1, 14.1; ESI: m/z = 397 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{18}H_{30}O_6NaS$: 397.1660, found: 397.1668.

4.1.9. (3*S*,4*S*,6*R*)-7-(Methoxymethoxy)-4,6-dimethylheptan-3-ol 19

Compound **18** (1.0 g, 2.67 mmol) was converted in 3 h into compound **19** (0.48 g, 88%) following the procedure adopted for compound **12**. $[\alpha]_D^{25} = -9.0$ (c 1, $CHCl_3$); IR (neat): ν_{max} 3453, 2960, 2928, 2879, 1461, 1312, 1109, 1044 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.57 (s, 2H), 3.33 (s, 3H), 3.44–3.28 (m, 3H), 1.87–1.75 (m, 1H), 1.64–1.39 (m, 5H), 0.95 (t, J = 7.4 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 96.5, 75.5, 73.01, 55.1, 37.5, 34.7, 30.6, 27.3, 18.1, 13.8, 10.6; ESI: m/z = 227 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{11}H_{24}O_3Na$: 227.1623, found: 227.1628.

4.1.10. (((3*S*,4*S*,6*R*)-7-(Methoxymethoxy)-4,6-dimethylheptan-3-yloxy)methyl)benzene 20

To a stirred suspension of NaH (0.14 g, 5.87 mmol) in dry THF (10 mL) at 0 °C was added a solution of compound **19** (0.4 g, 1.95 mmol) in dry THF (10 mL). The mixture was refluxed for 30 min and allowed to reach room temperature. Then benzyl bromide (0.25 mL, 2.05 mmol) was added and the mixture was again refluxed for 4 h. The reaction mixture was quenched by using ice and extracted with ether. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to afford the pure compound **20** (0.518 g, 90%) as a light yellow liquid. $[\alpha]_D^{25} = -13.0$ (c 0.5, $CHCl_3$); IR (neat): ν_{max} 2959, 2928, 2877, 1459, 1147, 1105, 1047 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33–7.21 (m, 5H), 4.54 (s, 2H), 4.49 (ABq, J = 11.3, 3.8 Hz, 2H), 3.34 (dd, J = 9.1, 5.3 Hz, 1H), 3.30 (s, 3H), 3.22 (dd, J = 9.1, 6.8 Hz, 1H), 3.16–3.08 (m, 1H), 1.89–1.71 (m, 2H), 1.63–1.44 (m, 4H), 0.94 (d, J = 6.8 Hz, 3H), 0.92 (t, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.3, 128.2, 127.5, 127.2, 96.3, 84.0, 72.8, 71.8, 55.0, 37.1, 32.7, 31.1, 23.4, 18.6, 15.5, 10.7; ESI: m/z = 317 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{18}H_{30}O_3Na$: 317.2092, found: 317.2084.

4.1.11. (2*R*,4*S*,5*S*)-5-(Benzyloxy)-2,4-dimethylheptan-1-ol 5

To a stirred solution of compound **20** (0.45 g 1.52 mmol) in MeOH (10 mL) was added a catalytic amount of *p*TSA. The reaction mixture was stirred at room temperature for 6 h. After completion of the reaction solid $NaHCO_3$ was added to neutralize the *p*TSA and filtered. The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc/pet-ether, 3:7) to afford pure compound **5** (0.33 g, 87%) as a colorless liquid. Compound **5** (0.332 g, 93%) was prepared from compound **29** (0.52 g 1.426 mmol) following the procedure described above. $[\alpha]_D^{25} = -1.8$ (c 1, $CHCl_3$); IR (neat): ν_{max} 3413, 2959, 2925, 2868, 1457, 1057 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.20 (m, 5H), 4.50 (ABq, J = 11.7 Hz, 2H), 3.42 (dd, J = 10.3, 4.4 Hz, 1H), 3.34 (dd, J = 10.3, 6.5 Hz, 1H), 3.18–3.10 (m, 1H), 1.88–1.76 (m, 1H), 1.66–1.44 (m, 5H), 0.92 (t, J = 7.3 Hz, 3H), 0.91 (d, J = 7.3 Hz, 3H), 0.90 (d, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.2, 128.2, 127.7, 127.3, 84.0, 71.8, 67.9, 36.2, 33.2, 32.6, 23.2, 17.7, 15.6, 10.6; ESI: m/z = 273 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{16}H_{26}O_2Na$: 273.1830, found: 273.1818.

4.1.12. (2*R*,3*S*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2-methylpentan-1-one 21

To a solution of (3.0 g, 11.30 mmol) thiazolidinethione propionate **10** in dry CH_2Cl_2 (50 mL) was added ($TiCl_4$ 1 M in CH_2Cl_2) at 0 °C (11.52 mL, 11.52 mmol) forming a red-orange slurry. After 5 min, DIPEA (2.16 mL, 12.66 mmol) was slowly added forming the characteristic enolate color (deep red). After 30 min at −78 °C, propionaldehyde (1.64 mL, 22.60 mmol) freshly distilled under N_2) in dry CH_2Cl_2 (20 mL) was added. Within 5 min, the color had faded to a pale brown color, indicating consumption of the enolate. The reaction mixture was quenched with saturated aqueous NH_4Cl solution. It was diluted with CH_2Cl_2, and the product was extracted with CH_2Cl_2 washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to afford the pure compound **21** (3.1 g, 85%) as a yellow viscous liquid. $[\alpha]_D^{25} = -32.5$ (c 2, $CHCl_3$); IR (neat): ν_{max} 3507, 2969, 2935, 2879, 1779, 1694, 1456, 1386, 1212, 1113, 971 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.22 (m, 5H), 5.33 (ap ddd, J = 10.5, 6.8, 3.8 Hz, 1H), 4.69 (dq, J = 6.8, 6.8 Hz, 1H), 3.94 (ddd, J = 7.5, 5.3, 2.3 Hz, 1H), 3.35 (dd, J = 12.1, 7.5 Hz, 1H), 3.2 (dd, J = 12.8, 3.8 Hz, 1H), 3.03 (dd, J = 13.6, 10.6 Hz, 1H), 2.88 (d, J = 11.3 Hz, 1H), 2.77–2.59 (br s, OH), 1.65–1.51 (m, 1H), 1.50–1.34 (m, 1H), 1.17 (d, J = 6.8 Hz, 3H), 0.98 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.5, 178.4, 136.3, 129.4, 128.8, 127.2, 72.4, 68.8, 42.1, 36.9, 31.7, 26.5, 10.4, 10.3; ESI: m/z = 346 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{16}H_{21}NO_2NaS_2$: 346.0911, found: 346.0913.

4.1.13. (2*S*,3*S*)-2-Methylpentane-1,3-diol 22

To a solution of **21** (2.7 g, 8.34 mmol) in MeOH (50 mL), $NaBH_4$ (0.79 g, 20.86 mmol) was added at 0 °C and stirred at the same temperature for 1 h. After the completion of reaction MeOH was removed under reduced pressure, the reaction mixture was quenched with saturated NH_4Cl solution, extracted with EtOAc, and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was Purified by silica gel column chromatography (EtOAc/pet-ether, 7:3) to afford the pure compound **22** (0.86 g, 88%) as viscous liquid. $[\alpha]_D^{25} = +1.0$ (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 3371, 2966, 2932, 2881, 1460, 1027, 967 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.74–3.66 (m, 3H), 2.48–2.20 (br s, OH, 1H), 1.83–1.71 (m, 1H), 1.57–1.39 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 75.8, 66.9, 38.6, 26.8, 10.5, 9.8.

4.1.14. (4*S*,5*S*)-4-Ethyl-5-methyl-2-phenyl-1,3-dioxane 23

To a solution of diol **22** (0.8 g, 6.77 mmol) in dry CH_2Cl_2 (20 mL) was added the dimethyl acetal of benzaldehyde (1.1 mL, 7.44 mmol) at 0 °C. To the reaction mixture was added a catalytic amount of *p*TSA and the reaction mixture was stirred at rt for 2 h. After completion of the reaction, the reaction mixture was quenched by adding a saturated solution of $NaHCO_3$ at 0 °C and the product was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to afford pure compound **23** (1.27 g, 91%) as a colorless liquid. $[\alpha]_D^{25} = -17.0$ (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 2966, 2935, 2877, 2848, 1458, 1396, 1370, 1166, 1114, 1073, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.26 (m, 5H), 5.44 (s, 1H), 4.02 (dabq, *J* = 11.3, 2.3 Hz, 2H), 3.78 (ddd, *J* = 8.3, 6.0, 2.3 Hz, 1H), 1.76–1.59 (m, 1H), 1.60–1.50 (m, 1H), 1.49–1.38 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.9, 128.6, 128.1, 126.0, 101.8, 81.3, 73.8, 31.3, 25.5, 10.9, 9.6; ESI: *m*/*z* = 245 $[M+K]^+$.

4.1.15. (2*S*,3*S*)-3-(Benzyloxy)-2-methylpentan-1-ol 24

To a solution of compound **23** (1.22 g, 5.91 mmol) in dry CH_2Cl_2 (40 mL) was added DIBAL-H (1.7 M in Toluene) at −15 °C (5.2 mL, 8.87 mmol) and the reaction mixture was stirred at same temperature while monitoring the reaction. After completion of the reaction quenched by the addition of a saturated solution of sodium potassium tartrate. The mixture was stirred for 2 h at rt. Then the product was extracted with EtOAc and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure; the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 3:7) to furnish pure compound **24** (1.10 g, 90%) as a clear liquid. $[\alpha]_D^{25} = -2.0$ (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 3422, 2966, 2934, 2876, 1457, 1094, 1064, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.21 (m, 5H), 4.55 (s, 2H), 3.63 (dd, *J* = 10.6, 7.5 Hz, 1H), 3.51 (dd, *J* = 10.6, 4.5 Hz, 1H), 3.41 (ddd, *J* = 7.6, 6.0, 3.8 Hz, 1H) 2.10–1.96 (m, 1H), 1.76–1.44 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4, 128.3, 127.4, 127.3, 83.5, 71.7, 66.0, 36.6, 22.7, 11.5, 10.5; ESI: *m*/*z* = 231 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{13}H_{20}O_2Na$: 231.1360, found: 231.1371.

4.1.16. (2*R*,3*S*)-3-(Benzyloxy)-2-methylpentanal 25

To an ice-cooled solution of 2-iodoxybenzoic acid (1.71 g, 6.10 mmol) in DMSO (3.6 mL, 50.81 mmol) was added a solution of alcohol **24** (1.06 g, 5.09 mmol) in dry CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 2 h and then filtered through a Celite pad and washed with ether. The combined organic filtrates were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The unstable crude aldehyde was used immediately for the next reaction.

4.1.17. (2*R*,3*S*,4*S*,5*S*)-1-((*S*)-4-Benzyl-2-thioxothiazolidin-3-yl)-5-(benzyloxy)-3-hydroxy-2,4-dimethylheptan-1-one 9

Aldehyde **25** (0.88 g, 4.27 mmol) was converted into compound **9** (1.47 g, 80%) using thiazolidinethione propionate **10** (1.03 g, 3.88 mmol)) following the procedure adopted for the preparation of compound **21**. $[\alpha]_D^{25} = +41.0$ (*c* 1.5, $CHCl_3$); IR (neat): ν_{max} 3453, 2868, 2934, 2876, 1695, 1455, 1344, 1257, 1162, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.19 (m, 10H), 5.37 (dddd, *J* = 10.7, 7.8, 3.9, 0.9 Hz, 1H), 4.78 (dq, *J* = 6.8, 1.9 Hz, 1H), 4.46 (Abq, *J* = 18.1, 10.6 Hz, 2H), 4.09 (dd, *J* = 9.7, 1.9 Hz, 1H), 3.91 (t, *J* = 6.8 Hz, 1H), 3.33 (dd, *J* = 10.7, 6.8 Hz, 1H), 3.27 (dd, *J* = 12.7, 2.9 Hz, 1H), 3.01 (dd, *J* = 13.6, 10.7 Hz, 1H), 2.88 (d, *J* = 11.7 Hz, 1H), 1.77–1.64 (m, 1H), 1.60–1.48 (m, 2H), 1.18 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.1, 177.7, 138.5, 136.3, 129.3, 129.1, 128.8, 128.3, 127.4, 127.2, 84.4, 74.7, 71.1, 68.8, 41.6, 36.8, 37.2, 31.4, 23.1, 14.4, 10.1, 7.6; HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{26}H_{33}NO_3NaS_2$: 494.1799, found: 494.1809.

4.1.18. (2*S*,3*R*,4*S*,5*S*)-5-(Benzyloxy)-2,4-dimethylheptane-1,3-diol 26

Compound **9** (1.4 g, 2.97 mmol) was converted into compound **26** (0.86 g, 90%) following the procedure adopted for the preparation of compound **22**. $[\alpha]_D^{25} = +12.1$ (*c* 2, $CHCl_3$); IR (neat): ν_{max} 3416, 2966, 2932, 2877, 1456, 1417, 1334, 1280, 1059, 971 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.26 (m, 5H), 4.56 (ABq, *J* = 18.1, 10.6 Hz, 2H), 4.16 (d, *J* = 5.3 Hz, 1H), 3.77–3.46 (m, 4H), 2.09–1.96 (m, 1H), 1.88–1.68 (m, 2H), 1.61–1.45 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4, 128.4, 127.6, 127.5, 84.6, 77.3, 71.4, 66.8, 37.8, 36.7, 23.0, 11.6, 10.2, 7.6; ESI: *m*/*z* = 289 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{16}H_{26}O_3Na$: 289.1779, found: 289.1787.

4.1.19. (2*S*,3*R*,4*S*,5*S*)-5-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)-2,4-dimethylheptan-3-ol 27

To a stirred solution of diol **26** (0.64 g, 2.40 mmol) and imidazole (0.49 g, 7.21 mmol) in dry CH_2Cl_2 (30 mL) was added TBDMS-Cl (0.36 g, 2.40 mmol) portion wise at 0 °C. The reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, the solvent was removed in vacuo and the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to furnish pure compound **27** (0.868 g, 95% yield) as a colorless liquid. $[\alpha]_D^{25} = +17.6$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3417, 2964, 2932, 2876, 1458, 1381, 1059, 1030, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.20 (m, 5H), 4.56 (s, 2H), 3.79–3.61 (m, 3H), 3.49–3.32 (m, 1H), 2.00–1.84 (m, 1H), 1.83–1.66 (m, 2H), 1.55–1.36 (m, 1H), 1.05–0.86 (m, 18H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.6, 128.3, 127.6, 127.5, 84.3, 77.3, 71.1, 67.4, 37.4, 36.7, 25.8, 25.6, 18.2, 12.0, 10.3, 8.0, −5.6, −5.5; ESI: *m*/*z* = 403 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ *m*/*z* calcd for $C_{22}H_{40}O_3NaSi$: 403.2644, found: 403.2632.

4.1.20. *O*-(2*S*,3*R*,4*R*,5*S*)-5-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)-2,4-dimethylheptan-3-yl *S*-methyl carbonodithioate 28

Compound **27** (0.8 g, 2.10 mmol) was converted into compound **28** (0.90 g, 91%) following the procedure adopted for the preparation of compound **16**. $[\alpha]_D^{25} = +5.1$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 2925, 2853, 1564, 1494, 1037, 943 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.20 (m, 5H), 6.00 (dd, *J* = 9.2, 3.2 Hz, 1H), 4.43

(ABq, J = 17.0, 11.5 Hz, 2H), 3.76 (dd, J = 10.2, 6.0 Hz, 1H), 3.43 (dd, J = 10.0, 7.2 Hz, 1H), 3.23 (ddd, J = 8.7, 5.5, 1.9 Hz, 1H), 2.57 (s, 3H), 2.31–2.11 (m, 2H), 1.87–1.68 (m, 1H), 1.56–1.40 (m, 1H), 1.01 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H), 0.95 (t, J = 6.9 Hz, 3H) 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 216.3, 139.4, 128.0, 127.4, 127.0, 87.6, 79.7, 71.4, 63.9, 38.1, 37.7, 31.7, 25.9, 23.9, 18.9, 15.1, 10.5, 10.0, −5.5; ESI: m/z = 493 $[M+Na]^+$.

4.1.21. ((2*R*,4*S*,5*S*)-5-(Benzyloxy)-2,4-dimethylheptyloxy)(*tert*-butyl)dimethylsilane 29

Compound **28** (0.85 g, 1.80 mmol) was converted into compound **29** (0.57 g, 87%) following the procedure adopted for the preparation of compound **6**. $[\alpha]_D^{25} = +4.1$ (c 1, $CHCl_3$); IR (neat): ν_{max} 2961, 2929, 2874, 1458, 1377, 1091, 1062 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.28 (m, 5H), 4.48 (ABq, J = 11.3 Hz, 2H), 3.42 (dd, J = 9.8, 5.3 Hz, 1H), 3.33 (dd, J = 9.8, 6.0 Hz, 1H), 3.16–3.08 (m, 1H), 1.99–1.87 (m, 1H), 1.70–1.57 (m, 1H), 1.53–1.40 (m, 4H), 0.98–0.85 (m, 18H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.3, 128.2, 127.7, 127.3, 84.5, 71.5, 68.0, 36.8, 33.3, 32.2, 25.9, 22.1, 18.3, 17.9, 15.3, 10.7, -5.3; ESI: m/z = 365 $[M+H]^+$. HRMS (ESI): $[M+H]^+$ m/z calcd for $C_{22}H_{41}O_2Si$: 365.2875, found: 365.2871.

4.1.22. (2*R*,4*S*,5*S*)-5-(Benzyloxy)-2,4-dimethylheptana1 30

Compound **5** (0.6 g, 2.39 mmol) was converted into compound **30** following the procedure adopted for the preparation of compound **25**. The unstable crude aldehyde was used immediately in the next reaction.

4.1.23. (4*R*,6*S*,7*S*)-7-(Benzyloxy)-4,6-dimethylnonan-3-one 31

To a suspension of Mg (0.120 g, 5.03 mmol) in dry THF (10 mL), EtBr (0.388 g, 5.032 mmol) was added dropwise under N_2 atmosphere at 0 °C. It was allowed to stir for 30 min, at room temperature. To this Grignard reagent, aldehyde **30** (0.250 g, 1.006 mmol) in dry THF (10 mL) was added at 0 °C. After completion of the reaction the reaction mixture was quenched with saturated aqueous NH_4Cl solution, and then filtered through a Celite pad and washed with ethyl acetate. The filtrate was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (EtOAc/pet-ether, 1:9) afforded alcohol as a diastereomeric mixture (0.252 g, 90%). The alcohol (0.25 g, 0.897 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise at 0 °C to an ice-cooled solution of 2-iodoxybenzoic acid (0.301 g, 1.077 mmol) in DMSO (0.382 mL, 5.60 mmol). The mixture was stirred at room temperature for 2 h and then filtered through a Celite pad and washed with ether. The combined organic filtrates were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/pet-ether, 1:19) to afford the pure compound **31** (0.228 g, 92%) as a colorless liquid. $[\alpha]_D^{25} = -18.0$ (c 0.5, $CHCl_3$); IR (neat): ν_{max} 2967, 2934, 2876, 1711, 1458, 1376, 1099, 1067 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.18 (m, 5H), 4.48 (s, 2H), 3.16–3.05 (m, 1H), 2.68–2.53 (m, 1H), 2.38 (q, J = 14.4, 7.6 Hz, 2H) 1.95–1.82 (m, 1H), 1.71–1.41 (m, 3H), 1.34–1.20 (m, 1H), 1.06 (d, J = 6.8 Hz, 3H), 1.01 (t, J = 7.6 Hz, 3H), 0.91 (t, J = 7.6 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 215.5, 139.0, 128.2, 127.7, 127.3, 84.3, 71.6, 43.9, 36.2, 33.9, 32.8, 22.9, 17.7, 15.0, 10.4, 7.7; ESI: m/z = 299 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{18}H_{28}O_2Na$: 299.1987, found: 299.1986.

4.1.24. (3*S*,4*S*,6*R*)-4,6-Dimethyl-7-oxononan-3-yl acetate 3'

To a stirred solution of **31** (0.08 g, 0.289 mmol) in anhydrous benzene (5 mL) was added catalytic amount of 10% palladium adsorbed on carbon and stirred under an H_2 atmosphere for 4 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure and then anhydrous Et_3N (2 mL), Ac_2O (1 mL), and catalytic amount of DMAP were added to residual **1′** at 0 °C. The reaction mixture was stirred for 0.5 h, and then quenched by adding water, and extracted with diethyl ether. The combined organic layers were washed with water and satd $NaHCO_3$ and brine solution and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to afford compound **3′** (0.052 g, 80%) as a colorless liquid. $[\alpha]_D^{25} = -4.8$ (c 1, $CHCl_3$); IR (neat): ν_{max} 2969, 2933, 1732, 1459, 1374, 1243, 1021, 963 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.71 (ddd, J = 8.7, 4.9, 3.9 Hz, 1H), 2.66 (td, J = 13.8, 6.8 Hz, 1H), 2.47 (dq, J = 17.7, 7.4 Hz, 1H), 2.36 (dq, J = 17.7, 7.4 Hz, 1H), 2.05 (s, 3H), 1.78–1.66 (m, 1H), 1.64–1.47 (m, 4H), 1.05 (d, J = 6.8 Hz, 3H), 1.03 (t, J = 7.4 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 214.6, 170.8, 77.6, 43.2, 36.3, 34.2, 33.5, 24.1, 21.0, 17.3, 14.6, 10.1, 7.7; ESI: m/z = 251 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{13}H_{24}O_3Na$: 251.1623, found: 251.1624.

4.1.25. (3*R*,4*S*,6*R*)-4,6-Dimethyl-7-oxononan-3-yl acetate 3

To a stirred solution of compound **31** (0.1 g, 0.361 mmol) in benzene (5 mL) was added 10% Pd/C and stirred under an H_2 atmosphere for 4 h at room temperature. After completion of the reaction the catalyst was removed by filtration, the solvent evaporated and then the crude product **1′** was used directly for the next reaction. PPh_3 (0.237 g, 0.904 mmol) and acetic acid (0.207 mL, 3.617 mmol) were added to a solution of the above compound **1′** in THF (5 mL). DEAD (0.143 mL, 0.723 mmol) was added dropwise to it at 0 °C. The mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, and the mixture was purified by silica gel column chromatography (EtOAc/pet-ether, 1:19) to afford pure compound **3** (0.049 g, 60%) as a pale yellow liquid. $[\alpha]_D^{25} = +12.5$ (c 1, $CHCl_3$); IR (neat): ν_{max} 2969, 2933, 1732, 1459, 1374, 1243, 1021, 963 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.63 (dt, J = 7.9, 4.9 Hz, 1H), 2.62 (ddq, J = 8.9, 6.9, 4.9 Hz, 1H), 2.47 (dq, J = 17.8, 6.9 Hz, 1H), 2.39 (dq, J = 17.8, 6.9 Hz, 1H), 2.04 (s, 3H), 1.86–1.78 (m, 1H), 1.63–1.46 (m, 4H), 1.09 (d, J = 6.9 Hz, 3H), 1.04 (t, J = 6.9 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 214.9, 170.9, 78.8, 43.7, 35.3, 34.0, 33.9, 23.2, 21.0, 18.0, 15.7, 9.9, 7.7; ESI: m/z = 251 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{13}H_{24}O_3Na$: 251.1623, found: 251.1613.

4.1.26. (3*R*,5*S*,6*S*)-6-(Benzyloxy)-3,5-dimethyloctan-2-one 32

Aldehyde **30** (0.25 g, 1.006 mmol) was converted into compound **32** (0.205 g, 90%) using MeI (0.313 g, 5.032 mmol) and dry ether as a solvent for Grignard reaction following the procedure adopted for the preparation of compound **31**. $[\alpha]_D^{25} = -35.0$ (c 0.5, $CHCl_3$); IR (neat): ν_{max} 2966, 2930, 2875, 1710, 1457, 1373, 1098 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33–7.18 (m, 5H), 4.48 (s, 2H), 3.12 (dt, J = 8.1, 4.5 Hz, 1H), 2.56 (ddq, J = 13.4, 9.6, 6.4 Hz, 1H), 2.05 (s, 3H), 1.94–1.82 (m, 1H), 1.63–1.42 (m, 4H) 1.08 (d, J = 6.9 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 213.1, 139.0, 128.2, 127.7, 127.3, 84.2, 71.6, 45.0, 35.9, 32.8, 27.6, 22.9, 17.4, 15.0, 10.5; ESI: m/z = 285 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{17}H_{26}O_2Na$: 285.1830, found: 285.1834.

4.1.27. (3*S*,4*S*,6*R*)-4,6-Dimethyl-7-oxooctan-3-yl acetate 4'

Compound **32** (0.107 g, 0.266 mmol) was converted into compound **4′** (0.046 g, 81%) following the procedure adopted for the preparation of compound **3′**. $[\alpha]_D^{25} = -30.1$ (c 1, $CHCl_3$); IR (neat): ν_{max} 2967, 2929, 1733, 1459, 1372, 1243, 1020, 960 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.73 (dt, J = 8.3, 5.3 Hz, 1H), 2.64 (sextet, J = 6.8 Hz, 1H), 2.10 (s, 3H), 2.06 (s, 3H) 1.72 (ddd, J = 13.6, 7.5,

6.0 Hz, 1H), 1.66–1.45 (m, 3H), 1.08 (d, J = 7.5 Hz, 3H), 1.10–0.99 (m, 1H), 0.89 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 212.4, 170.9, 77.6, 44.3, 36.1, 33.4, 27.9, 24.1, 21.0, 16.9, 14.4, 10.1; ESI: m/z = 237 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{12}H_{22}O_3Na$: 237.1466, found: 237.1456.

4.1.28. (3*R*,4*S*,6*R*)-4,6-Dimethyl-7-oxooctan-3-yl acetate 4

Compound **32** (0.1 g, 0.381 mmol) was converted into compound **4** (0.048 g, 59%) following the procedure adopted for the preparation of compound **3**. $[\alpha]_D^{25} = +19.8$ (c 1, $CHCl_3$); IR (neat): ν_{max} 2967, 2929, 1733, 1459, 1372, 1243, 1020, 960 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.64 (dt, J = 7.9, 4.9 Hz, 1H), 2.59 (ddq, J = 9.8, 6.9, 4.9 Hz, 1H), 2.12 (s, 3H), 2.05 (s, 3H) 1.84–1.77 (m, 1H), 1.67–1.48 (m, 3H), 1.12 (d, J = 6.9 Hz, 3H), 1.10–1.02 (m, 1H), 0.87 (d, J = 6.9 Hz, 3H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 212.4, 171.0, 78.8, 44.8, 35.3, 33.9, 27.7, 23.2, 21.0, 17.7, 15.6, 9.9; ESI: m/z = 237 $[M+Na]^+$. HRMS (ESI): $[M+Na]^+$ m/z calcd for $C_{12}H_{22}O_3Na$: 237.1466, found: 237.1458.

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References

1. Nishidha, R.; Fukami, H. *Mem. Coll. Agric., Kyoto Univ.* **1983**, *122*, 1–24.
2. Riley, R. G.; Silverstein, R. M.; Moser, J. C. *Science* **1974**, *183*, 760–762.
3. Rodin, J. O.; Silverstein, R. M.; Burkhoder, W. E.; Gorman, J. E. *Science* **1969**, *165*, 904–906.
4. Masuda, Y.; Fujitha, K.; Mori, K. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 1744–1750.
5. (a) Yadav, J. S.; Rao, C. S.; Chandrasekhar, S.; Rama Rao, A. V. *Tetrahedron Lett.* **1995**, *36*, 7717–7720; (b) Yadav, J. S.; Abraham, S.; Reddy, M. M.; Sabitha, G.; Sanker, A. R.; Kunwar, A. C. *Tetrahedron Lett.* **2001**, *42*, 4713–4716; (c) Yadav, J. S.; Reddy, K. B.; Sabitha, G. *Tetrahedron Lett.* **2004**, *45*, 6475–6476; (d) Yadav, J. S.; Reddy, K. B.; Sabitha, G. *Tetrahedron* **2008**, *64*, 1971; (e) Sabitha, G.; Yadagiri, K.; Chandrashekhar, G.; Yadav, J. S. *Synthesis* **2010**, 4307–4311; (f) Yadav, J. S.; Yadagiri, K.; Madhuri, Ch.; Sabitha, G. *Tetrahedron Lett.* **2011**, *52*, 4269–4272; (g) Sabitha, G.; Yadagiri, K.; Bhikshapathi, M.; Chandrashekhar, G.; Yadav, J. S. *Tetrahedron: Asymmetry* **2010**, *21*, 2524–2529.
6. Stork, G.; Takahashi, J. *J. Am. Chem. Soc.* **1977**, *99*, 1275–1276.
7. Phillips, K. D.; Zemlicka, J.; Horowitz, J. P. *Carbohydr. Res.* **1973**, *30*, 281–286.
8. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574–1585.
9. Ramana, C. V.; Srinivas, B.; Puranik, V. G.; Gurjar, M. K. *J. Org. Chem.* **2005**, *70*, 8216–8219.
10. (a) Crimins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775; (b) Crimins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.
11. Schreiber, S. L.; Wang, Z.; Schulte, G. *Tetrahedron Lett.* **1988**, *29*, 4085–4088.
12. Sánta, Z.; Nagy, J.; Nyitrai, J. *Tetrahedron: Asymmetry* **2006**, *17*, 3111–3127.