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Graphical Abstract

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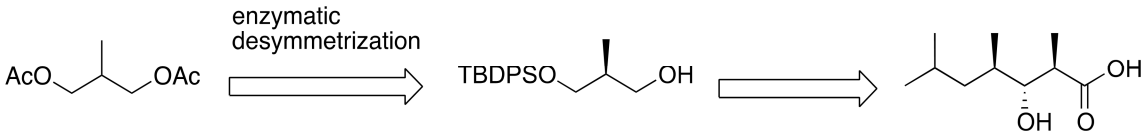

Preparation of (2*R*, 3*R*, 4*R*)-3-hydroxy-2,4,6-trimethylheptanoic acid via enzymatic desymmertization

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Abstract: Synthesis of a unique fatty acyl unit to build the *N*-terminus of callipeltin A and homophymine B is described. Our approach to access (2*R*, 3*R*, 4*R*)-3-hydroxy-2,4,6-trimethylheptanoic acid uses enzymatic hydrolysis for the desymmetrization of achiral acetate, followed by diastereoselective Roush crotylboration and Wittig olefination for the backbone construction.

Keywords: cyclicdepsipeptide, fatty acyl unit, enantioselective enzymatic desymmertization

1. Introduction

Cyclodepsipeptides callipeltin A (**1**) and homophymine B (**2**) were isolated from marine sponges *callipelta* sp. for **1** and *homophymia* sp. for **2** by the Zampella group.[1,2] These

molecules show potent inhibitory activities against C-C chemokine receptor type 5 (CCR5) which is employed as a coreceptor in HIV infection.[1] In addtition, callipeltin A (**1**) possesses antifungal activity against *Fusarium oxysporum*, *Helminthosporium sativum*, *Phytophtora hevea*, and *Candida albicans*. Homophymine B (**2**) exhibits IC_{50} values in the sub nM levels against various tumor cell lines (e.x. PC3, OV3, HL60, and HepG2).[3] The chemical structures of both peptides were determined by the combination of NMR and MS spectral analysis and Marfey's[4] or the GITC method.[5] Several unusual amino acids are incorporated within the cyclodepsipeptides, which are further modified by (2*R*, 3*R*, 4*R*)-3-hydroxy-2,4,6-trimethylheptanoic acid (HTH) (**3**) residues at the *N*-terminus. The total synthesis of callipeltin A (**1**) and homophymine B (**2**) have never been reported in the literature, although several synthetic studies of unusual amino acids and *N*-terminal fatty acid were revealed by Zampella, Lipton, etc. The characteristic structure of these peptides and their rare bioactivity motivated us to undertake the total synthesis of these molecules. Recently, our group achieved the synthesis of callipeltins B (**4**) and M (**5**) and the cyclic fragment of homophymine B (**2**) utilizing the combination of solution and solid phase approach.[6-8] Our next task is the construction of both natural peptides **1** and **2**. To achieve this, we have already synthesized two unusual amino acids [(2*S*, 3*S*, 4*R*)-dimethylglutamine (diMeGln)[9] and (2*R*, 3*R*, 4*S*)-4-amino-2,3-dihydroxyheptandioic acid (ADH)].[10] Therefore, we attempted the stereoselective synthesis of HTH (**3**), which is a component of callipeltin A (**1**) and homphymine B (**2**) **(Fig. 1)**.

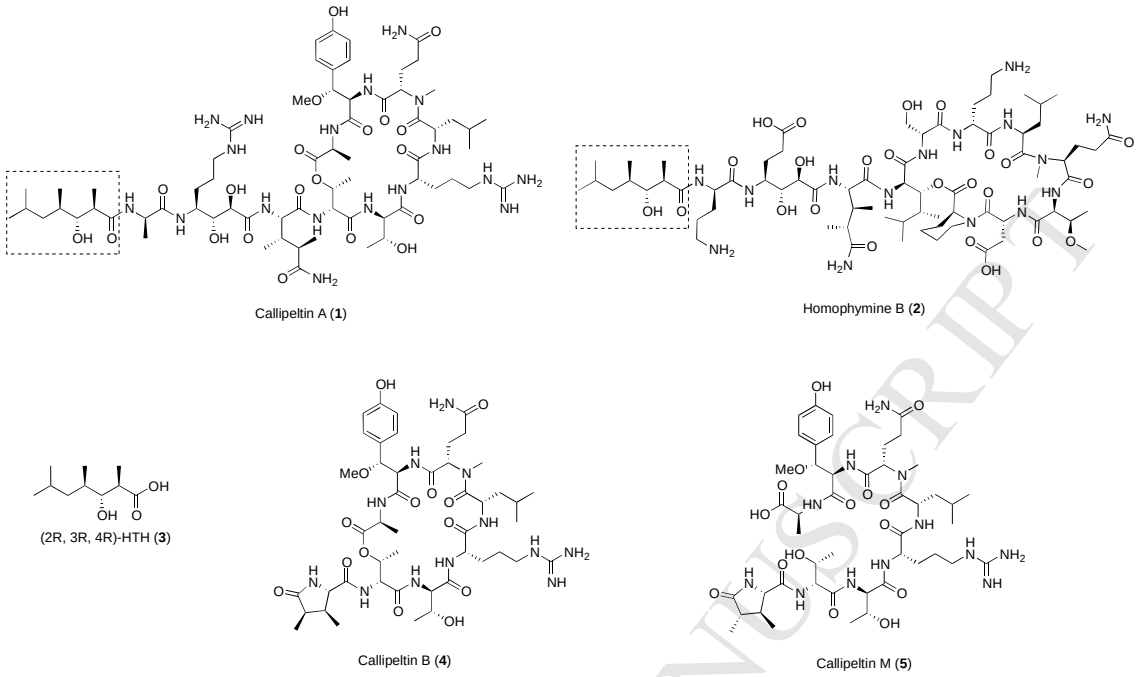


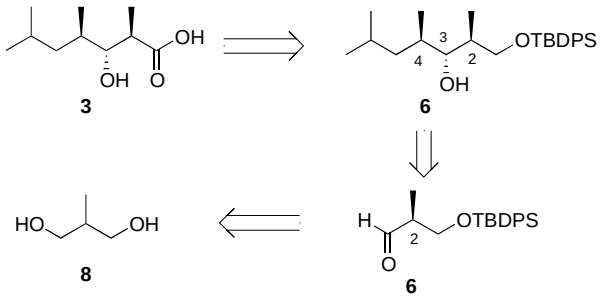
Fig. 1. Callipeltin A (**1**), Homophymine B (**2**), HTH (**3**), Callipeltin B (**4**), and M (**5**)

2. Results and discussion

Although the absolute configuration of HTH (**3**) was determined to be 2*R*, 3*R*, 4*S*, in an isolation study,[1] the Zampella group subsequently revised the stereochemistry of HTH (**3**) as 2*R*, 3*R*, 4*R* by comparison between the NMR spectra of isolated HTH (**3**) and those of a synthetic one, which was synthesized using Brown's crotylboration.[1,11] Later, the Lipton group attempted to determine the stereochemistry of HTH (**3**) by a synthetic approach.[12] Myers alkylation and Brown's crotylboration as a Lipton's strategy were employed to prepare four diastereoisomers of HTH (**3**). As a result, the spectroscopic data of all four diastereomers demonstrated the stereochemistries of the natural isomer to be 2*R*, 3*R*, 4*R*. In addition, this result was supported by Oku et al. Preparation of HTH-phynylglycine derivative and analyses of its stereochemistry by HPLC were reported.[13] In contrast, Zampella reported isolation of a series of homophymines of

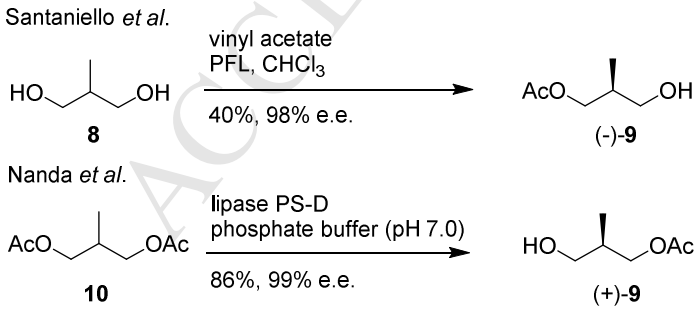
which bind five HTH analogs in 2009.[3] As the previous literatures to prepare HTH (**3**), there are two elegant synthetic routes by Zampella[11] and Lipton[12] groups. Zampella reported the synthesis of HTH (**3**) derived from (S)-2-methyl-3-hydroxypropionate, which is expensive as a starting material.[11] Lipton adopted Myers alkylation utilized ephedrine derivatives, and therefore removal process of the auxiliary group is needed to carry out the chiral materials.[12] Thus, we planned a synthetic route applicable for the synthesis of these analogs starting from cheap material as depicted in Scheme 1. In order to synthesize various analogs of HTH (**3**), the homoallylic alcohol **6** was used as the building block. The isopropyl unit of **3** was introduced by the oxidative cleavage and Wittig reaction of **6**. For construction of two consecutive stereocenters on C-3 and C-4 of the homoallylic alcohol **6**, we noted the crotylboration established by Roush and co-workers reported in 1987.[14] They found that crotylboration of the aldehyde (*R*)-**7** with chiral borate derived from diisopropyl tertrate gave the homoallylic alcohol (2*R*, 3*R*, 4*S*)-**6** preferentially.

Although aldehyde (*R*)-**7** derived from (*S*)-2-methyl-3-hydroxy propionate is known in the literature,[11] it is very expensive and not flexible as a starting material. Therefore, we decided to produce the remaining stereocenter of aldehyde **7** by a enantioselective enzymatic approach from a cheap starting material (**8**). This strategy is more flexible for the synthesis of different stereoisomers and analogs of HTH (**3**) and has advantage for the total synthesis of homophymines compered with previous reports (**Scheme 1**).



Scheme 1. Retrosynthetic analysis of HTH (**3**)

To prepare HTH (**3**) based on our strategy as mentioned above, the initial desymmetrizations of diol **8** and diacetate **10** were attempted by lipase. Previously, Santaniello *et al*. reported enzymatic mono-acetylation of diol **8** using PFL (*pseudomonas fluorescens* lipase) and vinyl acetate in chloroform to give (-)-**9** at a yield of 40% and 98% e.e.[15] Therefore, there is room for improvement in the chemical yield. On the other hand, Nanda *et al*. described the enzymatic desymmertization of diacetate **10** utilizing lipase PS-D in phosphate buffer (pH 7.0) to yield the monoacetate (+)-**9** (86%, 99% e.e.).[16] This is an elegant result, however lipase PS-D is not commercially available **(Scheme 2)**.



Scheme 2. Chemoenzymatic desymmetrization reaction of **8** and **10**

Thus, we firstly started to screen lipases in house with a variety of solvent

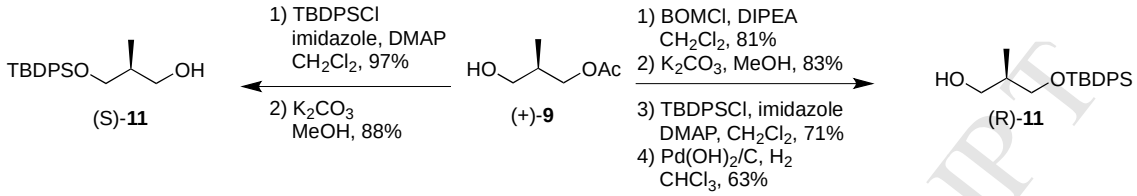
systems to give the mono acetylation of diol **8** utilizing 1.0 equiv of vinyl acetate as the acyl donor. Unfortunately, no satisfactory result was observed, although we attempted many combinations of various lipases, solvents, reaction times, and temperatures. On the other hand, the enantiomeric excess of monoacetate **9** was measured by chiral HPLC analysis after benzoylation and lipase mediated desymmetrization of diacetate **10** to give (+)-**9** was attempted (Table 1). Using lipase M AMANO 10, desymmetrization of **10** in H_2O proceeded to give the desired product (+)-**9** at a trace amount (entry 1). As acetic acid generated in this reaction decreased the solvent pH, the reaction mixture was treated in phosphate buffer pH 7.0 in the presence of lipase M AMANO 10. As a result, the chemical yield and enantiomeric excess were 50% and 59% e.e. (entry 2). Using some combinations of lipase catalysts, of which lipase PS AMANO or NOVOZYM 435 were active in preliminary screening, with the phosphate buffers (pH 6.0, 7.0, 8.0), each reaction proceeded smoothly with moderate enantioselectivities. Treatment of diacetate **10** with NOVOZYM 435 in a phosphate buffer solution (pH 8.0) resulted in 61% yield and 81% e.e. (entry 3). When using lipase PS AMANO, the reaction in phosphate buffer solution (pH 7.0) gave 85% e.e. (entries 4-6). In an attempt to adjust the reaction temperature for further improvement, it was found that lipase PS AMANO in a phosphate buffer solution of pH 7.0 at 1^{o}C provided satisfactory results (yield = 82%; e.e. = 95%) although this needed a reaction time for 84h (entry 7).[17] It is noted that this reaction did not proceed at -10 ^{o}C to recover diacetate **10** (entry 8). We have successfully developed high enantioselective desymmetrization for diacatate **10** to afford primary alcohol (+)-**9** with a common popular and cheap lipase. We found that lipase PS AMANO works even at 1 ^{o}C and this reaction was carried out on a 10 g scale to deliver the product at a reproducible yield and enantioselectivity. This result

suggested that the process could be applied to other substrates to obtain chiral compounds **(Table 1)**.[18]

Table 1. Asymmetric saponification of diacetate **10**.

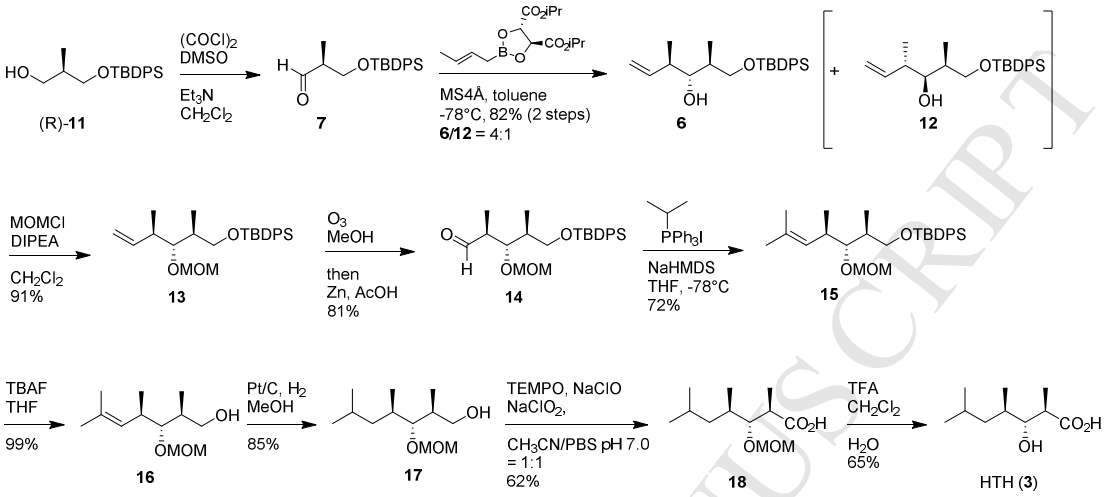
entry	enzyme	Solvent	temp. (°C)	time (h)	yield (%)	e.e. (%)
1	lipase M AMANO 10	H_2O	r.t.	11	9.3	75
2	lipase M AMANO 10	phosphate buffer pH 7.0	r.t.	23	50	59
3	NOVOZYM 435	phosphate buffer pH 8.0	r.t	2	61	81
4	lipase PS AMANO	phosphate buffer pH 6.0	r.t.	5.5	36	68
5	lipase PS AMANO	phosphate buffer pH 7.0	r.t.	2	48	85
6	lipase PS AMANO	phosphate buffer pH 8.0	r.t.	2	61	81
7	lipase PS AMANO	phosphate buffer pH 7.0	1	84	82	95
8	lipase PS AMANO	phosphate buffer pH 7.0/acetone =(3/2)	-10	18.5	trace	n.d.

Next, we prepared two optical isomers of 3-(tert-butyldiphenylsiloxy)-2-methylpropanol (**11**) to apply them to the synthesis of HTH analogs (Scheme 3). The free hydroxyl group in optical active (+)-**9** was a protected BOM group in the treatment with BOMCl in 81% yield. The acetate group was removed with K_2CO_3 in MeOH. Protection of the primary alcohol with TBDPSCl followed by hydrogenation of the BOM group with $Pd(OH)_2/C$ catalyst afforded the TBDPS protected product (*R*)-**11**. (*S*)-**11** was synthesized via protection as silyl ether and deprotection of the acetate group. The optical rotation of our synthetic (*R*) and (*S*)-**11**, R:$[\alpha]_D^{25}$ = +5.5 and S:$[\alpha]_D^{25}$ = -3.5, were nearly identical to the those in the literature (lit. R-**11**:$[\alpha]_D$ = +3.9 to +6.3 and lit. S-**11**:$[\alpha]_D$ = -4.3 to -6.0) (**Scheme 3**).[19,20]



Scheme 3. Synthesis of both optical isomers of alcohol **11**

Finally, we attempted the synthesis of HTH (**3**). After the oxidation of (*R*)-**11** under the Swern condition, the resulting aldehyde (*R*)-**7** was transformed to (3*R*, 4*R*, 5*S*)-**6** and (3*S*, 4*S*, 5*S*)-**12** as a 4 to 1 mixture by Roush crotylboration with (*E*, *S*, *S*)-type chiral borate (82% yields from (*R*)-**11**).[12] After separation of the mixture by silica gel column chromatography, the NMR data of (3*R*, 4*R*, 5*S*)-**6** and (3*S*, 4*S*, 5*S*)-**12** were identical to those of Roush's previous report.[14] The hydroxyl group of homoallylalcohol **6** was protected as the MOM ether to afford compound **13** in 91% yield. Oxidative cleavage of olefin **13** followed by Wittig olefination with the condition of isopropyltriphenylphosphonium iodide/NaHMDS/THF afforded tri-substituted alkene **15** in 58% yield over 2 steps. Deprotection of silyl ether of compound **15** using TBAF proceeded smoothly to give alcohol **16** in quantitative yield. **17** was derived from **16** by hydrogenation in the presence of a Pt/C catalyst. After the oxidation of **17** with TEMPO/$NaClO/NaClO_2$ in CH_3CN/pH 7.0 phosphate buffer (1:1), TFA-mediated deprotection of the MOM group in **18** was carried out to give HTH (**3**) in 40% yield over 2 steps. The spectroscopic data of synthetic HTH (**3**) overlapped with those of the revised HTH (**3**) reported by Lipton[12] and the HTH fragment of a natural product (**Scheme 4**).[1]



Scheme 4. Stereoselective synthesis of HTH (**3**).

3. Conclusion

We achieved efficient asymmetric synthesis of HTH (**3**), the *N*-terminus component of callipeltin A (**1**) and homophymine B (**2**). Our synthetic method features chemoenzymatic desymmetrization to prepare chiral alcohol (+)-**9** and Roush crotylboration as the key steps. This method is flexible and applicable to other analogues.

4. Experimental

4.1. General information.

Optical rotations were determined with a JASCO DIP-371 polarimeter at the sodium D line. IR spectra of sample were obtained as films with a JASCO FT-IR 460 spectrometer. ^{1}H (400 and 500 MHz) and ^{13}C NMR (100 and 125 MHz) were determined on a JNM-ECX400, JNM-ECX500. Chemical shifts are reported in ppm with reference to

tetramethylsilane [^{1}H NMR: $CDCl_3$ (0.00)], or solvent signals [^{1}H NMR: $CDCl_3$ (7.26), D_2O (4.79), MeOH-d_4 (3.30); ^{13}C NMR: $CDCl_3$ (77.16), MeOH-d_4 (50.05)]. Low-resolution mass spectra were recorded on a JEOL AccuTOF JMS-T100LC (ESI-MS). Analytical TLC was performed on Merck Silica gel $60F_{254}$. Crude products were purified by columm chromatography on Silica Gel 60N [Kanto, particle size, (spherical, neutral) 63-210 μm or 100-200 μm. HPLC system (monitored at 254 nm) equipped with DAICEL CHIRALCEL OD-H (0.46 cm ϕ × 25 cm) using 0.3% 2-propanol/Hexane.

4.2. (*R*)-3-Hydroxy-2-methylpropylacetate (9): To a solution of 1,3-diacetoxy-2-methylpropane (**10**) (8.53 g, 49.0 mmol) in 0.5 M phosphate buffer pH 7.0 (200 ml) at 1 °C was added lipase PS Amano (200 mg), and the reaction was stirring for 84h. After lipase was removed by filtration, mother liquid was extracted with AcOEt. The organic layer was washed with brine and $NaHCO_3$ aq., and dried over magunesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography (Hexane:AcOEt = 3:1) to give compound **9** (5.33 g, 40.3 mmol, 82%, 95% e.e.) as a colorless oil. $[\alpha]_D^{29}$ +5.5 (*c* 1.00, $CHCl_3$), {lit[15] $[\alpha]_D^{20}$ +10.0 (*c* 1.00, $CHCl_3$)}. IR (film) νmax cm^{-1}: 3447, 2964, 2882, 2360, 2341, 1738, 1469, 1369, 1244, 1038, 992, 950, 907, 607, 439 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (3H, d, *J* = 7.0 Hz), 2.02-1.93 (1H, m), 2.03 (1H, br), 2.07 (3H, s), 3.53-3.47 (2H, m), 4.04 (1H, dd, *J* = 11.5, 6.5 Hz), 4.11 (1H, dd, *J* = 11.5, 5.0 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.4, 20.7, 35.2, 64.0, 66.2, 171.6 ppm. HRMS-EI: m/z $[M-H]^-$ calcd for $C_6H_{11}O_3$: 131.0708; found: 131.0731.

4.3. (*R*)-3-(*tert*-Butyldiphenylsiloxy)-2-methylpropanol (*R*)-11: To a solution of

(*R*)-3-hydroxy-2-methylpropylacetate (**4**) (2.98 g, 22.5 mmol) in CH_2Cl_2 at 1 °C was added DIPEA (67.5 mmol, 11.8 ml) and BOMCl (33.8 mmol, 4.64 ml), and the reaction was stirring for 10h. The mixture was quenched with water and aqueous layer extracted with CH_2Cl_2. The organic layer was washed with brine, and dried over magunesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography (Hexane:AcOEt = 6:1) to give (*R*)-3-benzyloxymethoxy-2-methylpropylacetate (4.60 g, 18.2 mmol, 81%) as a colorless oil. $[\alpha]_D^{26}$ -0.20 (*c* 1.00, $CHCl_3$). IR (film) νmax cm^{-1}: 2960, 2880, 1738, 1497, 1455, 1379, 1366, 1243, 1174, 1111, 1043, 738, 699, 455 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.99 (3H, d, *J* = 6.5 Hz), 2.03 (3H, s), 2.07-2.14 (1H, m), 3.48-3.54 (2H, m), 4.01 (1H, dd, *J* = 11.0, 6.5 Hz), 4.08 (1H, dd, *J* = 11.5, 6.5 Hz), 4.59 (2H, s), 4.74 (2H, s), 7.27-7.31 (1H, m), 7.34-7.35 (4H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 21.0, 33.3, 66.4, 69.4, 69.8, 94.8, 127.8, 127.9, 128.5, 137.9, 171.2 ppm. HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{14}H_{20}O_4Na$: 275.1259; found: 275.1257. To a solution of (*R*)-3-benzyloxymethoxy-2-methylpropylacetate (1.50 g, 5.95 mmol) in MeOH at 0°C was added K_2CO_3 (2.98 mmol, 412 mg), and the reaction was stirring for 8h. The solvent was removed under reduced pressure and the crude residue was added to water. The aqueous layer extracted with AcOEt. The organic layer was washed with brine, and dried over magunesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography (Hexane:AcOEt = 3:1) to give benzyloxymethoxy-2-methylpropanol (1.04 g, 4.95 mmol, 83%) as a colorless oil. $[\alpha]_D^{25}$ -7.3 (*c* 1.00, $CHCl_3$). IR (film) νmax cm^{-1}: 3421, 2927, 2878, 2064, 1953, 1869, 1810, 1739, 1646, 1497, 1455, 1379, 1170, 1042, 737, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.92 (3H, d, J = 7.0 Hz), 1.97-2.04 (1H, m), 2.33 (1H, br), 3.54 (1H, dd, *J* = 9.5, 8.0 Hz), 3.59-3.60 (2H, m), 3.64 (1H, dd, *J* = 9.5, 5.0 Hz), 4.60 (2H, s), 4.75 (2H, s),

7.28-7.32 (1H, m), 7.35-7.36 (4H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 35.8, 67.1, 69.6, 72.3, 94.9, 127.9, 128.0, 128.6, 137.8 ppm. HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{12}H_{18}O_3Na$: 233.1154; found: 233.1153. To a solution of (*S*)-3-benzyloxymethoxy-2-methylpropanol (1.04 g, 4.95 mmol) in CH_2Cl_2 at 0°C was added imidazole (14.9 mmol, 1.01g), DMAP (cat.), and TBDPSCl (5.45 mmol, 1.42 ml) and the reaction was stirring for 12h. The mixture was quenched with water and aqueous layer extracted with CH_2Cl_2. The organic layer was washed with brine, and dried over magunesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography (Hexane:AcOEt = 10:1) to give (*R*)-3-benzyloxymethoxy-1-(*tert*-butyldiphenylsiloxy)-2-methylpropane (1.58 g, 3.52 mmol, 71%) as a colorless oil. $[\alpha]_D^{23}$ +4.4 (*c* 1.00, $CHCl_3$). IR (film) νmax cm^{-1}: 3069, 2957, 2930, 2857, 1959, 1888, 1823, 1774, 1589, 1471, 1428, 1390, 1157, 1111, 1047, 823, 738, 700, 613 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99 (3H, d, *J* = 6.5 Hz), 1.07 (9H, s), 1.98-2.04 (1H, m), 3.54 (1H, dd, *J* = 10.0, 6.5 Hz), 3.61-3.68 (3H, m), 4.59 (2H, s), 4.75 (2H, s), 7.27-7.31 (1H, m), 7.33-7.35 (4H, m), 7.37-7.45 (6H, m), 7.67-7.69 (4H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 19.4, 27.0, 36.4, 65.9, 69.3, 70.3, 94.9, 127.4, 127.7, 128.0, 128.5, 129.7, 134.0, 135.7, 138.1 ppm. HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{28}H_{36}O_3SiNa$: 471.2331; found: 471.2361. To a solution of (*R*)-3-benzyloxymethoxy-1-(*tert*-butyldiphenylsiloxy)-2-methylpropane (1.58 g, 3.52 mmol) in $CHCl_3$ was added $Pd(OH)_2/C$ (cat.) and the suspension was stirring for 4h. The reaction mixture was filtered and evaporated in vacuo. The residue was purified by column chromatography (Hexane:AcOEt = 6:1) to give (*R*)-3-(*tert*-Butyldiphenylsiloxy)-2-methylpropanol {(*R*)-**11**} (729 mg, 2.22 mmol, 63%) as a colorless oil. $[\alpha]_D^{26}$ +5.5 (*c* 1.00, $CHCl_3$). IR (film) νmax cm^{-1}: 3358, 3071, 2958,

2930, 2857, 1959, 1892, 1824, 1589, 1471, 1427, 1390, 1361, 1261, 1187, 1111, 1038, 938, 823, 801, 739, 701, 665, 613 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (3H, d, *J* = 6.5 Hz), 1.05 (9H, s), 1.96-2.02 (1H, m), 2.54-2.55 (1H, br), 3.59 (1H, dd, *J* = 10.5, 8.5 Hz), 3.67 (2H, t, *J* = 6.0 Hz), 3.72 (1H, dd, *J* = 9.5, 4.0 Hz), 7.38-7.45 (6H, m), 7.66-7.68 (4H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.3, 19.2, 26.9, 37.4, 67.8, 68.8, 127.5, 129.8, 133.2, 135.6 ppm. HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{20}H_{28}O_2SiNa$: 351.1756; found: 351.1753. Optical purity was determined as 95% ee by HPLC using chiral column {DAICEL CHIRALCEL OD-H (0.46 cm ϕ × 25 cm), elution with 0.3% 2-propanol/Hexane} after conversion into the corresponding benzoate (Rt= 7.95 min).

4.4. (*S*)-3-(*tert*-Butyldiphenylsiloxy)-2-methylpropanol (*S*)-11: To a solution of (*S*)-3-benzyloxymethoxy-2-methylpropanol (3.09 g, 23.4 mmol) in CH_2Cl_2 at 0°C was added imidazole (46.8 mmol, 3.19 g), DMAP (cat.), and TBDPSCl (35.1 mmol, 9.13 ml) and the reaction was stirring for 12h. The mixture was quenched with water and aqueous layer extracted with CH_2Cl_2. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography (Hexane:AcOEt = 20:1) to give (*S*)-3-acetoxy-1-(*tert*-butyldiphenylsiloxy)-2-methylpropane (8.46 g, 22.8 mmol, 97%) as a colorless oil. $[\alpha]_D^{26}$ -0.5 (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (3H, d, *J* = 7.0 Hz), 1.04 (9H, s), 2.00 (3H, m), 3.54-3.61 (2H, m), 4.04 (2H, dd, *J* = 11.0, 6.0 Hz), 4.11 (2H, dd, *J* = 11.0, 6.0 Hz), 7.36-7.43 (6H, m), 7.65 (2H, d, *J* = 7.0 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 19.4, 21.0, 27.0, 35.3, 65.3, 66.2, 127.7, 129.7, 133.7, 135.7, 171.2 ppm. To a solution of

(*S*)-3-acetoxy-2-methylpropylacetate (2.03 g, 5.48 mmol) in MeOH was added K_2CO_3 (2.74 mmol, 379 mg) and the reaction was stirring for 10h. The solvent was removed under reduced pressure and the crude residue was added to water. The aqueous layer extracted with ether. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography (Hexane:AcOEt = 3:1) to give (*S*)-3-(*tert*-Butyldiphenylsiloxy)-2-methylpropanol {(*S*)-**11**} (1.68 g, 5.11 mmol, 93%) as a colorless oil. $[\alpha]_D^{25}$ -3.5 (*c* 1.00, $CHCl_3$). The spectroscopic data of *S*-**11** were identical to those of *R*-**11**.

4.5. (3*R*, 4*R*, 5*S*)-6-(*tert*-Butyldiphenylsiloxy)-4-hydroxy-3,5-dimethylhexanene (6) and **(3*S*, 4*S*, 5*S*)-6-(*tert*-Butyldiphenylsiloxy)-4-hydroxy-3,5-dimethylhexanene (12):** Oxalyl chloride (20 mmol, 1.72 ml) was added in dry CH_2Cl_2 at -78°C. DMSO (40.0 mmol, 2.84 ml) was added to the solution. After 10 min, alcohol **11** (3.29 g, 10.0 mmol) was added dissolving in dry CH_2Cl_2. The reaction mixture was kept at same temperature for 10 min. Then Et_3N (60.0 mmol, 8.39 ml) was added to the solution and it was allowed to warm room temperature. After 15 min, The mixture was quenched with water and aqueous layer extracted with CH_2Cl_2. The organic layer was washed with brine, and dried over magnesium sulfate, and evaporated in vacuo to give aldehyde **7** as a colorless oil. **7**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 (9H, s), 1.09 (3H, d, *J* = 7.5 Hz), 2.53-2.60 (1H, m), 3.84 (1H, dd, *J* = 11.0, 7.0 Hz), 3.89 (1H, dd, *J* = 10.5, 5.5 Hz), 7.37-7.45 (6H, m), 7.63-7.64 (4H, m), 9.76 (1H, d, *J* = 1.5 Hz) ppm. To a solution of (2*E*, 4*S*, 5*S*)-1,3,2-dioxaborolane-4,5-dicarboxylic acid 2-butenyl-4,5-bis(1-methylethyl) ester in toluene was added MS4Å (3.0 g) in -78°C. Aldehyde **6** was added dissolving in toluene slowly. After 2.5h, The reaction was

quenched with 1M NaOH aq. and filtered. The mother liquid was extracted with ether. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The crude product was purified by column chromatography (Hexane) to give **12** (0.67 g, 1.75 mmol, 18%) and **6** (2.48 g, 6.48 mmol, 65%) as a colorless oil. **6**: $[\alpha]_D^{24}$ +15.8 (*c* 2.00, $CHCl_3$), {lit[14c] $[\alpha]_D^{20}$ +26.2 (*c* 0.80, $CHCl_3$)}. IR (film) νmax cm^{-1}: 3499, 3071, 2960, 2931, 2857, 2359, 1960, 1889, 1826, 1736, 1637, 1589, 1471, 1427, 1325, 1281, 1111, 1005, 912, 822, 740, 701, 613 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.80 (3H, d, *J* = 6.5 Hz), 1.05 (9H, s), 1.11 (3H, d, *J* = 7.0 Hz), 1.80-1.87 (1H, m), 2.34-2.40 (1H, m), 3.43 (1H, dt, *J* = 8.0, 3.5 Hz), 3.53, (1H, d, *J* = 3.5 Hz), 3.68 (1H, dd, *J* = 10.5, 7.5 Hz), 3.73 (1H, dd, *J* = 10.0, 4.5 Hz), 5.04-5.09 (2H, m), 5.94 (1H, ddd, *J* = 17.5, 11.0, 8.5 Hz), 7.39-7.46 (6H, m), 7.67-7.69 (4H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 17.9, 19.2, 26.9, 37.9, 41.3, 69.1, 79.9, 115.3, 127.9, 130.0, 133.0, 135.7, 140.0 ppm. HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{24}H_{34}O_2SiNa$: 405.2226; found: 405.2243. **12**: $[\alpha]_D^{25}$ +5.8 (*c* 1.00, $CHCl_3$) ,{lit[14c] $[\alpha]_D^{20}$ +4.9 (*c* 2.80, $CHCl_3$)}. IR (film) νmax cm^{-1}: 3507, 3071, 2961, 2930, 2857, 1959, 1889, 1824, 1638, 1589, 1472, 1428, 1390, 1111, 997, 914, 823, 739, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.95 (6H, d, *J* = 7.0 Hz), 1.06 (9H, s), 1.81-1.84 (1H, m), 2.26-2.30 (1H, m), 2.44 (1H, d, *J* = 2.5 Hz), 3.59 (1H, dt, *J* = 8.5, 2.0 Hz), 3.72 (2H, d, *J* = 5.0 Hz), 5.08-5.12 (2H, m), 5.82 (1H, ddd, *J* = 19.0, 10.5, 8.0 Hz), 7.37-7.45 (6H, m), 7.66-7.69 (4H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.7, 16.9, 19.4, 27.0, 36.8, 41.9, 68.6, 76.3, 115.5, 127.8, 129.8, 133.3, 135.7, 142.0 ppm. HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{24}H_{34}O_2SiNa$: 405.2226; found: 405.2238.

4.6. (3*R*, 4*R*, 5*S*)-6-(*tert*-Butyldiphenylsiloxy)-4-methoxymethoxy-3,5-dimethyl

hexanene (13): To a solution of **6** (428 mg, 1.12 mmol) in CH_2Cl_2 at 0°C was added DIPEA (11.2 mmol, 1.92 ml) and MOMCl (5.60 mmol, 0.421 ml), and the reaction was stirring for 3d. The reaction was quenched with water and aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine, and dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography (Hexane) to give compound **13** (0.435 mg, 1.02 mmol, 91%) as a colorless oil. $[\alpha]_D^{22}$ +2.3 (*c* 1.00, $CHCl_3$). IR (film) νmax cm^{-1}: 3071, 2960, 2931, 2889, 2857, 2359, 2342, 1958, 1889, 1825, 1738, 1639, 1589, 1472, 1428, 1389, 1361, 1308, 1146, 1111, 1034, 916, 823, 739, 701, 613 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (3H, d, *J* = 7.0 Hz), 1.05 (3H, d, *J* = 7.5 Hz), 1.07 (9H, s), 1.84-1.90 (1H, m), 2.41-2.47 (1H, m), 3.26 (3H, s), 3.33 (1H, dd, *J* = 7.5, 4.0 Hz), 3.62 (1H, dd, *J* = 10.0, 7.0 Hz), 3.72 (1H, dd, *J* = 10.0, 4.5 Hz), 4.53 (1H, d, *J* = 6.5 Hz), 4.62 (1H, d, *J* = 7.0 Hz), 4.97-4.98 (1H, m), 5.00, (1H, s), 5.82 (1H, ddd, *J* = 18.5, 10.0, 8.0 Hz), 7.35-7.43 (6H, m), 7.65-7.68 (4H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6, 18.1, 19.4, 27.1, 38.9, 40.4, 56.0, 65.7, 85.2, 98.4, 114.6, 127.7, 129.0, 134.0, 135.8, 140.7 ppm. HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{26}H_{38}O_3SiNa$: 449.2488; found: 449.2481.

4.7. (4*R*, 5*R*, 6*S*)-7-(*tert*-Butyldiphenylsiloxy)-5-methoxymethoxy-2,4,6-trimethyl-2-heptene (15): Ozone was bubbled through a solution of alkene **13** (807 mg, 1.89 mmol) in MeOH at -78°C. After 11h, Zn (28.4 mmol, 1.86 g) and AcOH (3.78 mmol, 0.216 ml) were added to the reaction mixture. The suspension was filtered and evaporated in vacuo. The crude product was purified by column chromatography (Hexane:AcOEt = 40:1) to give aldehyde **14** (662 mg, 1.54 mmol, 63%) as a colorless oil. **14**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (3H, d, *J* = 7.2 Hz), 1.05 (9H, s), 1.11 (3H, d, *J* = 7.2 Hz),

1.96-2.02 (1H, m), 2.69-2.72 (1H, m), 3.27 (3H, s), 3.61-3.69 (2H, m), 3.82 (1H, dd, *J* = 6.4, 4.0 Hz), 4.54 (1H, d, *J* = 6.8 Hz), 4.64 (1H, d, *J* = 6.8 Hz), 7.35-7.39 (6H, m), 7.62-7.65 (4H, m), 9.72 (1H, d, *J* = 2.0 Hz) ppm. To a solution of isopropyltriphenylphosphonium iodide (4.62 mmol, 2.00 g) in THF at -78°C was added 1.9 M NaHMDS/THF (4.62 mmol, 2.43 ml) over 20 min. The reaction mixture was allowed to warm room temperature, and aldehyde **14** was added dissolving in THF. After 1.5h, the mixture was quenched with NH_4Cl aq. and water at 0°C. The aqueous layer was extracted with AcOEt. The organic solvent was washed brine and dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography (Hexane:AcOEt = 40:1) to give compound **15** (507 mg, 1.11 mmol, 72%) as a colorless oil. $[\alpha]_D^{26}$ -4.7 (*c* 0.085, $CHCl_3$). IR (film) νmax cm^{-1}: 3071, 2959, 2927, 2856, 2359, 1956, 1888, 1827, 1733, 1471, 1428, 1362, 1260, 1147, 1111, 1035, 920, 739, 701 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.93 (3H, d, *J* = 7.0 Hz), 0.95 (3H, d, *J* = 6.5 Hz), 1.06 (9H, s), 1.55 (3H, overlapped), 1.66 (3H, s), 1.81-1.86 (1H, m), 2.55-2.60 (1H, m), 3.26 (3H, m), 3.30 (1H, dd, *J* = 7.5, 4.0 Hz), 3.59 (1H, dd, *J* = 10.0, 6.5 Hz), 3.71 (1H, dd, *J* = 10.5, 4.5 Hz), 4.54 (1H, d, *J* = 7.0 Hz), 4.61 (1H, d, *J* = 7.0 Hz), 5.10 (1H, d, *J* = 9.5 Hz), 7.28-7.42 (6H, m), 7.64-7.67 (4H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6, 18.0, 18.9, 19.4, 26.0, 27.1, 29.8, 34.9, 39.4, 56.0, 65.8, 85.7, 98.4, 126.7, 127.6, 129.6, 134.0, 135.8 ppm. HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{28}H_{42}O_3SiNa$: 477.2801; found: 477.2767.

4.8. (4*R*, 5*R*, 6*S*)-7-Hydroxy-5-methoxymethoxy-2,4,6-trimethyl-2-heptene (16): To a solution of **15** (507 mg, 1.11 mmol) in THF at 0°C added 1.0 M TBAF/THF solution (2 ml). After 12h, the mixture was quenched with H_2O. The aqueous layer was extracted

with AcOEt. The combined organic layer was washed with NH_4Cl aq. and dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography (Hexane:AcOEt = 10:1) to give compound **16** (237 mg, 1.10 mmol, 99%) as a colorless oil. $[\alpha]_D^{26}$ -67.2 (*c* 0.50, $CHCl_3$). IR (film) νmax cm^{-1}: 3447, 2963, 2927, 2359, 2341, 1732, 1716, 1671, 1451, 1376, 1213, 1146, 1096, 1034, 983, 920, 849 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.95 (3H, d, *J* = 7.0 Hz), 0.98 (3H, d, *J* = 6.5 Hz), 1.61 (3H, d, *J* = 1.0 Hz), 1.69 (3H, d, *J* = 1.5 Hz), 1.70-1.76 (1H, m), 2.60-2.67 (1H, m), 2.92 (1H, br), 3.30 (1H, dd, *J* = 8.0, 3.5 Hz), 3.43 (3H, s), 3.47 (1H, dd, *J* = 11.5, 3.5 Hz), 3.84 (1H, dd, *J* = 11.5, 3.5 Hz), 4.67-4.71 (2H, m), 5.09 (1H, dt, *J* = 10.0, 1.5 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.1, 18.6, 25.9, 35.4, 38.1, 65.1, 87.5, 99.2, 125.5, 131.8 ppm. HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{12}H_{24}O_3Na$: 239.1623; found: 239.1631.

4.9. (2*S*, 3*R*, 4*R*)-3-Methoxymethoxy-2,4,6-trimethyl-1-heptanol (17): To a solution of **16** (60.8 mg, 0.278 mmol) in MeOH was added Pt/C (cat.) and the suspension was stirring for 2h under H_2 atmosphere. The reaction mixture was filtered and evaporated to give compound **17** (51.3 mg, 0.235 mmol, 85%) as a colorless oil. $[\alpha]_D^{25}$ -35.5 (*c* 0.40, $CHCl_3$). IR (film) νmax cm^{-1}: 3435, 2957, 2929, 1466, 1383, 1367, 1212, 1142, 1093, 1036, 987, 919, 665, 455, 439 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.83 (3H, d, *J* = 7.0 Hz), 0.91 (3H, d, *J* = 7.0 Hz), 0.95 (3H, d, *J* = 7.0 Hz), 0.97 (3H, d, *J* = 7.5 Hz), 1.08-1.20 (2H, m), 1.08-1.20 (2H, m), 1.58-1.66 (1H, m), 1.75-1.81 (1H, m), 1.83-1.88 (1H, m), 3.31 (1H, dd, *J* = 8.5, 3.0 Hz), 3.43 (3H, s), 3.52 (1H, dd, *J* = 11.5, 4.0 Hz), 3.84 (1H, dd, *J* = 11.5, 3.5 Hz), 4.67-4.71 (2H, m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.4, 17.3, 21.4, 24.3, 25.4, 33.0, 36.9, 39.9, 56.3, 65.5, 88.2, 99.0 ppm. HRMS-ESI:

m/z $[M+Na]^+$ calcd for $C_{12}H_{26}O_3Na$: 241.1780; found: 241.1762.

4.10. (2*R*, 3*R*, 4*R*)-3-Methoxymethoxy-2,4,6-trimethylheptanoic acid (18): To a solution of alcohol **17** (7.9 mg, 36.2 μmol) in CH_3CN was added TEMPO (cat.), 0.5 M phosphate buffer pH 7.0, $NaClO_2$ (72.4 μmol, 6.6 mg), and NaClO aq. (2 ml). After 2h, 2M HCl aq. was added to the mixture (pH = 1.0). The aqueous layer was extracted with AcOEt. The AcOEt layer was extracted with 1M NaOH aq., and 2M HCl aq. was added to the aqueous layer again (pH = 1.0). The organic solvent was washed with brine and dried over magnesium sulfate and evaporated to give the compound **18** (5.3 mg, 22.8 μmol, 62%) as a colorless oil. $[\alpha]_D^{26}$ + 9.1 (*c* 0.27, $CHCl_3$). IR (film) νmax cm^{-1}: 3178, 2956, 2930, 2359, 2341, 1711, 1463, 1418, 1382, 1367, 1297, 1244, 1215, 1141, 1096, 1033, 976, 936, 920, 840, 666, 453, 405 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.83 (3H, d, *J* = 7.0 Hz), 0.91 (3H, d, *J* = 6.0 Hz), 0.94 (3H, d, *J* = 6.5 Hz), 1.11-1.20 (1H, m), 1.21 (3H, d, *J* = 6.5 Hz), 1.58-1.65 (1H, m), 2.76-2.82 (1H, m), 3.38 (3H, s), 3.55 (1H, dd, *J* = 6.0, 4.0 Hz), 4.66-4.70 (2H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 16.0, 21.4, 24.0, 25.2, 32.8, 40.6, 42.4, 56.1, 85.6, 97.9, 179.6 ppm. HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{12}H_{24}O_4Na$: 255.1572; found: 255.1599.

4.11. (2*R*, 3*R*, 4*R*)-3-Hydroxy-2,4,6-trimethylheptanoic acid [HTH] (3): To a solution of **18** (5.3 mg, 22.8 μmol) in CH_2Cl_2 was added TFA (0.5 ml). After 10h, the mixture was evaporated, and ether and 1M NaOH aq. was added to the residue. Then 2M HCl aq. was added to water phase (pH = 1.0) and water layer was extracted with AcOEt. The combine organic phase was washed with brine and dried over magnesium sulfate and evaporated to give HTH (**3**) (2.8 mg, 14.9 μmol, 65%) as a colorless oil.

$[\alpha]_D^{25}$ + 15.7 (*c* 0.14, $CHCl_3$), {lit[12] $[\alpha]_D^{25}$ + 14.9 (*c* 0.4, $CHCl_3$)}. IR (film) νmax cm^{-1}: 3424, 2957, 2927, 2360, 1713, 1462, 1384, 1289, 1261, 1202, 1133, 1082, 987, 963, 666 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.84 (3H, d, *J* = 6.0 Hz), 0.92 (3H, d, *J* = 6.5 Hz), 0.95 (3H, d, *J* = 6.5 Hz), 1.10-1.16 (1H, m), 1.25 (3H, d, *J* = 7.0 Hz), 1.64-1.70 (2H, m), 2.73 (dq, *J* = 7.5, 7.5 Hz), 3.48 (1H, dd, *J* = 6.0, 5.0 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.7, 16.6, 21.2, 24.3, 25.1, 33.4, 39.4, 42.1, 78.2, 180.6 ppm. HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{10}H_{20}O_3Na$: 211.1310; found: 211.1311.

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