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Synthetic studies on homophymine A: stereoselective synthesis of (2*R*,3*R*,4*R*,6*R*)-3-hydroxy-2,4,6-trimethyloctanoic acid

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ABSTRACT

An efficient and highly stereocontrolled synthesis of (2*R*,3*R*,4*R*,6*R*)-3-hydroxy-2,4,6-trimethyloctanoic acid, the β-hydroxy acid unit that acylates the N-terminus of homophymine A, has been devised starting from iodoethane and (*S*,*S*)-pseudoephedrine propionamide in 9 steps and 36% average overall yield. Comparison of the ^{1}H and ^{13}C NMR and optical rotation data of the resulting β-hydroxy acid with the natural fragment unambiguously verifies the configurational assignment as (2*R*,3*R*,4*R*,6*R*).

1. Introduction

Potent HIV inhibitory cyclic depsipeptides have recently been described from Lithistida marine sponges. Peptides in this family include callipeltins from *Callipelta* sp.,[1] neamphamide A from *Neamphius huxleyi*,[2] papuamides,[3] and theopapuamides[4] from the Papua New Guinea collections of *Theonella* species, and mirabamides from the Micronesian sponge *Siliquariaspongia mirabilis*.[5]

Homophymine A (**1**), isolated in our laboratory from a New Caledonian collection of the marine sponge *Homophymia* sp.,[6] represents the latest, very recent example of this class. In addition to antifungal and cytotoxic activities, all these compounds displayed potent antiviral properties.

Distinguishing structural characteristics of this family of peptides include a preponderance of unusual amino acid residues, such as (2*S*,3*S*,4*R*)-3,4-dimethylglutamine (diMeGln), common to all metabolites and unique N-terminal polyketide derived moieties.

(2*R*,3*R*,4*R*,6*R*)-3-Hydroxy-2,4,6-trimethyloctanoic acid **2** (HTMOA) is a key component of homophymine A whose structure was determined by interpretation of spectroscopic data, acid hydrolysis, and Mosher analysis.[6] The HTMOA moiety, that is simply a C-1 homolog of the β-hydroxy acid end group in callipeltin A and neamphamide A (3-hydroxy-2,4,6-trimethylheptanoic acid, HTMHA), has already been found as the end group of the related theopapuamide.[4]

Although three asymmetric syntheses of (2*R*,3*R*,4*R*)-HTMHA residue have been reported,[7–9] only one synthetic strategy was explored for (2*S*,3*S*,4*R*,6*R*)-diastereomer of the fatty acid moiety of homophymine A, found as a component of the aliphatic depside bourgeanic acid.[10]

2. Results and discussion

As a part of our efforts to total synthesis of homophymine A herein we report an asymmetric synthesis of (2*R*,3*R*,4*R*,6*R*)-3-hydroxy-2,4,6-trimethyloctanoic acid **2** starting from commercially available iodoethane.

Our retrosynthetic analysis of 3-hydroxy-2,4,6-trimethyloctanoic acid **2** is shown in Figure 1. We envisaged that the stereoselective construction of the key C-2/C-3 bond would arise through an asymmetric crotylboration on aldehyde **4**. The substrate aldehyde (*R*,*R*)-**4** could in turn be made in high enantiomeric purity using the diastereoselective alkylation chemistry of Myers.[11]

The required precursor (*R*)-**7** was made efficiently from iodoethane according to Myers's protocol. Commercial pseudoephedrine propionamide (*S*,*S*)-**6** was alkylated with iodoethane to give (*S*,*S*,*R*)-**8** as a highly viscous oil in 88% yield (Scheme 1). The diasteroisomeric purity of amide (*S*,*S*,*R*)-**8** was determined to be >98% by employing Myers' NMR-based method.[12] Therefore the crude alkylation product was subjected to cyclization with triflic anhydride-pyridine and ^{1}H NMR analysis of oxazolium product revealed a 98% diastereomeric purity of the starting amide. Conversion of the tertiary amide to the primary alcohol with lithium amidotrihydroborate[13] (LAB) and subsequent treatment with iodine and triphenylphosphine furnished compound **7** in 72% yield over two steps.

(2*R*)-2-Methyl-1-iodobutane **7** was transformed into aldehyde **4** in a three-step sequence (82% yield for three steps) involving alkylation of pseudoephedrine propionamide (*S*,*S*)-**6**, LAB reduction of amide function of **5** followed by Ley oxidation of the obtained primary alcohol (*R*,*R*)-**10**.[14]

Brown's crotylboration[15] was selected as the key step for the assembly of the C2–C3 *anti*-propionate unit in β-hydroxy acid **2** (Scheme 2). Thus, aldehyde **4** was reacted with the allyl borane derived from (−)-*B*-methoxydiisopinocampheyl borane and (*E*)-

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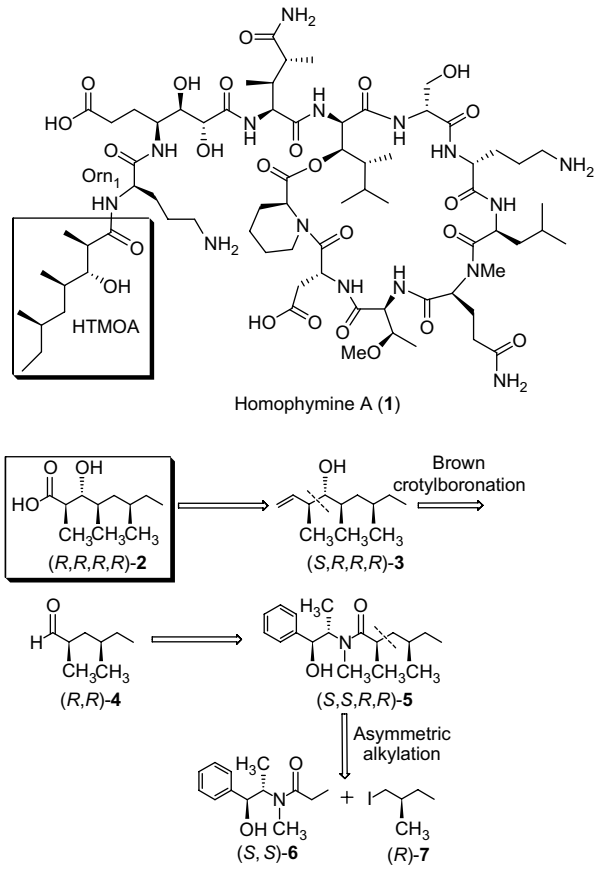
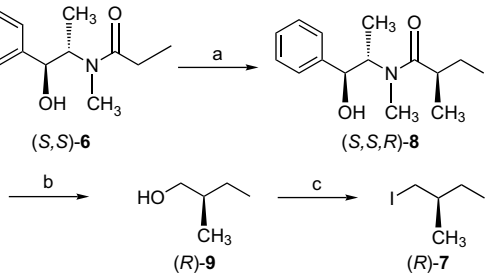


Figure 1. Retrosynthetic analysis of (2*R*,3*R*,4*R*,6*R*)-3-hydroxy-2,4,6-trimethyloctanoic acid **2**.

butene to give the *anti*-homoallylic alcohol (*S*,*R*,*R*,*R*)-**3**. The diastereomeric purity of **3** was >98% as judged by the NMR spectra of the crude reaction mixture. We encountered difficulties in separating **3** in acceptable yield from the isopinocampheol arising from the reaction. Thus, crude **3** was converted into the TBS-protected derivative **11**, which was easily separated from the protected isopinocampheol by silica gel chromatography (92% yield of **11** from **4**). Treatment of (*S*,*R*,*R*,*R*)-**11** with catalytic osmium tetraoxide and stoichiometric sodium periodate followed by in situ oxidation of the resultant aldehyde with sodium chlorite occurred with concomitant removal of the silyl protecting group giving carboxylic acid (*R*,*R*,*R*,*R*)-**2** in 75% yield (Scheme 2).

The complete overlap of the NMR data of the synthetic derivative **2** with those of the corresponding natural unit (see Experimental section), obtained through acid hydrolysis of parent



Scheme 1. Reagents and conditions: (a) LDA, LiCl, THF, −78 °C→rt, iodoethane, 13 h, 88%; (b) *n*-BuLi, DIPA, THF, −78 °C→0 °C, $BH_3{\cdot}NH_3$, (*S*,*S*,*R*)-**8**, rt, 2 h, 85%; (c) iodine, imidazole, triphenylphosphine, CH_2Cl_2, rt, 85%.

peptide followed by dichloromethane extraction, unambiguously defined the (2*R*,3*R*,4*R*,6*R*) configuration.

Further confirmation of the absolute stereochemistry of natural **2** was obtained from comparison of specific rotation data (synthetic **2**: $[\alpha]_D$=+21.2, *c* 7.3, $CHCl_3$); natural HTMOA: $[\alpha]_D$=+21.8 (*c* 5.4, $CHCl_3$).

In conclusion, the stereochemistry of the β-hydroxy acid unit that acylates the N-terminus of the cyclodepsipeptide homophymine A (**1**) was definitively confirmed by asymmetric synthesis. Furthermore, our synthesis is short (nine steps from the commercially available iodoethane and pseudoephedrine propionamide (*S*,*S*)-**6**), efficient (36% overall yield), and amenable to scale-up.

3. Experimental

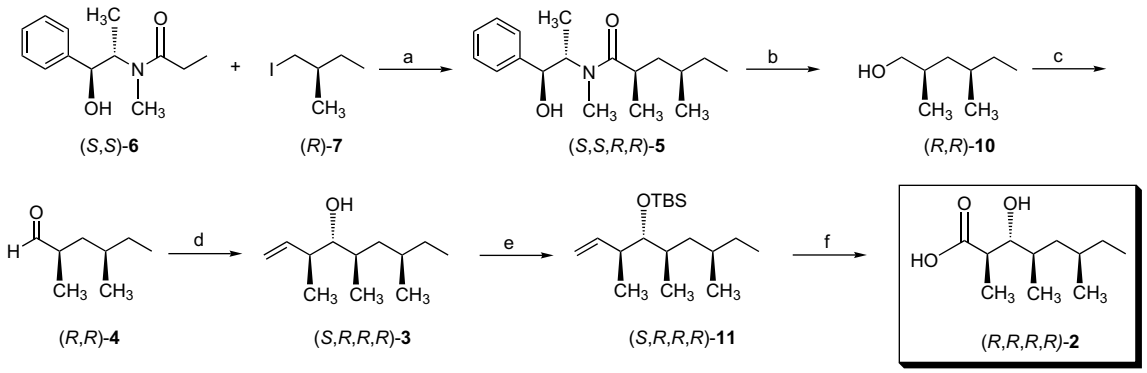
3.1. General

Specific rotations were measured on a Perkin–Elmer 243 B polarimeter. High-resolution ESI-MS spectra were performed with a Micromass QTOF Micromass spectrometer. ESI-MS experiments were performed on an Applied Biosystem API 2000 triple-quadrupole mass spectrometer. NMR spectra were obtained on Varian Inova 500 and Varian Mercury VX 400, δ (ppm), *J* in hertz, spectra referred to $CDCl_3$ as internal standards (δ_H=7.26). HPLC was performed using a Waters Model 510 pump equipped with Waters Rheodine injector and a differential refractometer, model 401.

Solvents and reagents were used as supplied from commercial sources with the following exceptions. Tetrahydrofuran, toluene, dichloromethane and diisopropylamine were distilled from calcium hydride immediately prior to use. All reactions were monitored by TLC on silica gel plates (Machery, Nagel). Crude products were purified by column chromatography on silica gel 70–230 mesh. All reactions were carried out under an argon atmosphere using dry glassware.

3.2. (2*R*)-*N*-[(1*S*,2*S*)-2-Hydroxy-1-methyl-1-phenylethyl]-*N*-methyl-2-methylbutanamide 8

A solution of *n*-butyllithium in hexane (2.5 M, 17.0 mL, 42.6 mmol, 2.10 equiv) was added via cannula to a suspension of lithium chloride (6.02 g, 142.1 mmol, 7.00 equiv) and diisopropylamine (6.60 mL, 46.7 mmol, 2.30 equiv) in dry THF (20.0 mL) at −78 °C. The resulting suspension was warmed to 0 °C briefly and then was cooled to −78 °C. An ice-cooled solution of amide (*S*,*S*)-**6** (4.50 g, 20.3 mmol, 1.00 equiv) in dry THF (50.0 mL) was added via cannula. The mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, and at 23 °C for 5 min. The mixture was cooled to 0 °C, and iodoethane (6.50 mL, 81.2 mmol, 4.00 equiv) was added via cannula. The reaction was removed from the cold bath and stirred for 13 h at room temperature. The yellow solution was quenched by the addition of saturated aqueous ammonium chloride solution (30 mL), and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give a yellow oil. Purification of the residue by silica gel chromatography (70% hexane–ethyl acetate) afforded amide (*S*,*S*,*R*)-**8** as a highly viscous, colorless oil (4.45 g, 88%). R_f (40% hexane/ethyl acetate) 0.43; $[\alpha]_D$= +9.0 (*c* 0.9, chloroform); IR ($CHCl_3$): 3379, 2959, 1620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.31 (5H, m, Ph), 4.61 (1H, t, *J* 7.2 Hz, C*H*OH), 4.41 (1H, m, C*H*N), 4.09 (1H, br s, O*H*), 2.85 (3H, s, N*Me*), 2.53 (1H, m, COC*H*Me), 1.62 (1H, m, C*Ha*HbMe), 1.37 (1H, m, CHa*Hb*Me), 1.14 (3H, d, *J* 6.8 Hz, NCH*Me*), 1.09 (3H, d, *J* 6.8 Hz, COCH*Me*), 0.84 (3H, t, *J* 7.4 Hz, CH_2*Me*); ^{13}C NMR (100 MHz, $CDCl_3$), * denotes minor rotamer peaks, δ: 179.1, 142.5, 128.6*, 128.2 (×2), 127.4, 126.8*, 126.3 (×2), 76.4, 75.4*, 57.8, 38.2, 37.5*, 33.1, 26.9, 17.6*, 16.9, 15.4*, 14.5, 12.0*, 11.9; HRMS (ESI): calcd for $C_{15}H_{24}NO_2$: 250.1807; found 250.1824 $[M+H]^+$.



Scheme 2. Reagents and conditions: (a) LDA, LiCl, THF, −78 °C→rt, (*R*)-**7**, 13 h, 95%; (b) *n*-BuLi, DIPA, THF, −78 °C→0 °C, $BH_3{\cdot}NH_3$, (*S*,*S*,*R*,*R*)-**5**, rt, 2 h, 88%; (c) TPAP, NMO, 4 Å MS, CH_2Cl_2, 1 h, 98%; (d) *t*-BuOK, *trans*-2-butene, *n*-BuLi, −78 °C→−57 °C, (−)-*B*-methoxydiisopinocampheylborane, $BF_3{\cdot}OEt_2$, (*R*,*R*)-**4**, −78 °C, 4 h; (e) TBSCl, imidazole, DMF, 24 h, 92%, two steps; (f) OsO_4, NMO, 1 h, $NaIO_4$, 1.5 h, $NaClO_2$, H_2NSO_3H, 2 h, dioxane–H_2O, 75%.

3.3. (2*R*)-2-Methylbutanol 9

A solution of *n*-butyllithium in hexane (2.5 M, 27.0 mL, 67.5 mmol, 3.90 equiv) was added to a solution of diisopropylamine (10.3 mL, 72.7 mmol, 4.20 equiv) in THF (20.0 mL) at −78 °C. The resulting solution was stirred at −78 °C for 10 min, then warmed to 0 °C, and held at that temperature for 10 min. Borane–ammonia complex (2.14 g, 69.2 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 °C for 15 min and then was warmed at room temperature. After 15 min, the suspension was cooled to 0 °C. A solution of amide (*S*,*S*,*R*)-**8** (4.30 g, 17.3 mmol, 1.00 equiv) in dry THF was added via cannula, and the reaction mixture was warmed to 23 °C, held at that temperature for 2 h, and then cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous HCl (30 mL) solution. The mixture was stirred for 2 h at 0 °C and then extracted with diethyl ether (3×30 mL). The combined organic extracts were washed sequentially with 3 N aqueous HCl solution (25 mL), 2 N aqueous NaOH solution (25 mL), and brine. The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by silica gel chromatography (99% hexane–ethyl acetate) afforded alcohol (*R*)-**9** as a highly viscous, colorless oil (1.30 g, 85%). R_f (80% hexane/ethyl acetate) 0.60; $[\alpha]_D$= −9.8 (*c* 10.2, chloroform); ^{1}H NMR (400 MHz, CD_3OD) *δ*: 3.55 (2H, d, *J* 6.7 Hz, *CH*$_2$OH), 1.51 (1H, m, C*H*Me), 1.35 (1H, m, C*H*aHbMe), 1.18 (3H, d, *J* 6.7 Hz, CH*Me*), 1.00 (1H, m, CHa*H*bMe), 0.91 (3H, t, *J* 7.5 Hz, CH_2*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 67.9, 34.6, 18.9, 14.8, 13.5; HRMS (ESI): calcd for $C_5H_{13}O$: 89.0966; found 89.0952 $[M+H]^+$.

3.4. (*R*)-1-Iodo-2-methylbutane 7

Imidazole (1.39 g, 20.4 mmol, 1.5 equiv) and iodine (4.66 g, 18.4 mmol, 1.35 equiv) were added sequentially to a solution of triphenylphosphine (4.28 g, 16.3 mmol, 1.20 equiv) in CH_2Cl_2 (20 mL) at 23 °C. A solution of alcohol (*R*)-**9** (1.20 g, 13.6 mmol, 1.00 equiv) in CH_2Cl_2 (5 mL) was added to the resulting fine suspension via cannula. After 2 h, dichloromethane was removed in vacuo. Purification of the residue by silica gel chromatography (95% hexane–ethyl acetate) afforded iodide (*R*)-**7** as a highly viscous, colorless oil (2.29 g, 85%); R_f (hexane) 0.99; $[\alpha]_D$= −8.6 (*c* 12.3, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 3.20 (2H, m, *CH*$_2$I), 1.39 (2H, m, C*H*Me, C*H*aHbMe), 1.26 (1H, m, CHa*H*bMe), 0.97 (3H, d, *J* 7.4 Hz, CH*Me*), 0.89 (3H, t, *J* 7.4 Hz, CH_2*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 36.3, 29.1, 20.1, 17.5, 11.3; HRMS (ESI): calcd for $C_5H_{12}I$: 198.9984; found 198.9972 $[M+H]^+$.

3.5. (2*R*,4*R*)-*N*-[(1*S*,2*S*)-2-Hydroxy-1-methyl-1-phenylethyl]-*N*-methyl-2,4-dimethylhexanamide 5

A solution of *n*-butyllithium in hexane (2.5 M, 8.08 mL, 20.2 mmol, 4.00 equiv) was added via cannula to a suspension of lithium chloride (2.72 g, 64.1 mmol, 12.7 equiv) and diisopropylamine (3.08 mL, 21.8 mmol, 4.31 equiv) in dry THF (10.0 mL) at −78 °C. The resulting suspension was warmed to 0 °C briefly and then was cooled to −78 °C. An ice-cooled solution of amide (*S*,*S*)-**6** (2.35 g, 10.6 mmol, 2.10 equiv) in dry THF (30.0 mL) was added via cannula. The mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, and at 23 °C for 5 min. The mixture was cooled to 0 °C, and (*R*)-(+)-1-iodo-2-methylbutane (1.00 g, 5.05 mmol, 1.00 equiv) was added via cannula. The reaction was removed from the cold bath and stirred for 13 h at room temperature. The yellow solution was quenched by the addition of saturated aqueous ammonium chloride solution (30 mL), and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give a yellow oil. Purification of the residue by silica gel chromatography (70% hexane–ethyl acetate) afforded amide (*S*,*S*,*R*,*R*)-**5** as a highly viscous, colorless oil (1.40 g, 95%). R_f (50% hexane/ethyl acetate) 0.47; $[\alpha]_D$= +6.2 (*c* 1.2, chloroform); IR ($CHCl_3$): 3379, 2959, 1620 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.38–7.30 (5H, m, Ph), 4.62 (1H, t, *J* 6.7 Hz, C*H*OH), 4.38 (1H, br s, O*H*), 4.11 (1H, m, C*H*N), 2.86 (3H, s, N*Me*), 2.70 (1H, m, COC*H*Me), 1.70 (1H, m, C*H*Me), 1.36 (1H, m, C*H*aHbMe), 1.35 (1H, m, C*H*aHb), 1.27 (1H, m, CHa*H*b), 1.15 (3H, d, *J* 6.5 Hz, NCH*Me*), 1.08 (3H, d, *J* 6.8 Hz, COCH*Me*), 1.06 (1H, m, CHa*H*bMe), 0.87 (3H, t, *J* 7.3 Hz, CH_2*Me*), 0.77 (3H, d, *J* 6.4 Hz, CH*Me*); ^{13}C NMR (100 MHz, $CDCl_3$), * denotes minor rotamer peaks, *δ*: 179.3, 142.8, 141.7*,128.8*, 128.5 (×2), 127.6, 127.2*, 126.6 (×2), 76.6, 75.3*, 59.2*, 58.3, 41.5*, 41.4, 34.3, 33.5, 32.3*, 32.2, 29.9, 19.6*, 19.4, 18.9*, 18.1, 15.7*, 14.6, 11.5; HRMS (ESI): calcd for $C_{18}H_{30}NO_2$: 292.2277; found 292.2288 $[M+H]^+$.

3.6. (2*R*,4*R*)-2,4-Dimethylhexanol 10

A solution of *n*-butyllithium in hexane (2.5 M, 6.96 mL, 17.4 mmol, 3.90 equiv) was added to a solution of diisopropylamine (2.65 mL, 18.7 mmol, 4.20 equiv) in THF (5 mL) at −78 °C. The resulting solution was stirred at −78 °C for 10 min, then warmed to 0 °C, and held at that temperature for 10 min. Borane–ammonia complex (550 mg, 17.8 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 °C for 15 min and then was warmed at room temperature. After 15 min, the suspension was cooled to 0 °C. A solution of amide (*S*,*S*,*R*,*R*)-**5** (1.30 g, 4.46 mmol, 1.00 equiv) in dry THF was added via cannula, and the reaction

mixture was warmed to 23 °C, held at that temperature for 2 h, and then cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous HCl solution. The mixture was stirred for 2 h at 0 °C and then extracted with diethyl ether (3×25 mL). The combined organic extracts were washed sequentially with 3 N aqueous HCl solution (25 mL), 2 N aqueous NaOH solution (25 mL), and brine. The combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the residue by silica gel chromatography (99% hexane–ethyl acetate) afforded alcohol (*R*,*R*)-**10** as a highly viscous, colorless oil (510 mg, 88%). R_f (5% ethyl acetate/hexane) 0.33; $[\alpha]_D$= +4.0 (*c* 8.7, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 3.52 (1H, dd, *J* 5.1, 10.4 Hz, C*H*aHbOH), 3.37 (1H, dd, *J* 6.8, 10.4 Hz, CHa*H*bOH), 1.71 (1H, m, $HOCH_2CH$Me), 1.54 (1H, m, C*H*Me), 1.42 (1H, m, C*H*aHb), 1.36 (1H, m, CHa*H*b), 1.31 (1H, m, C*H*aHbMe), 1.05 (1H, m, CHa*H*bMe), 0.92 (3H, d, *J* 6.7 Hz, $HOCH_2CH$*Me*), 0.87 (3H, t, *J* 7.3 Hz, CH_2*Me*), 0.86 (3H, d, *J* 6.4 Hz, CH*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 68.6, 40.5, 33.1, 31.5, 29.0, 19.8, 17.3, 11.1; HRMS (ESI): calcd for $C_8H_{19}O$: 131.1436; found 131.1448 $[M+H]^+$.

3.7. (2*R*,4*R*)-2,4-Dimethylhexanal 4

To a stirred solution of (*R*,*R*)-**10** (500 mg, 3.84 mmol, 1.00 equiv), *N*-methylmorpholine-*N*-oxide (899 mg, 7.68 mmol, 2.00 equiv), and 4 Å molecular sieves (1.92 g) in dry CH_2Cl_2 (4.00 mL), a catalytic amount of tetrapropylammonium perruthenate (67.5 mg, 0.19 mmol, 0.05 equiv) was added. After stirring the reaction mixture at room temperature for 1 h, it was filtered through Celite washing with diethyl ether to obtain 481 mg of aldehyde (*R*,*R*)-**4** (98%), immediately used for Brown's reaction. R_f (20% ethyl acetate/hexane) 0.43; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 9.57 (1H, d, *J* 2.5 Hz, C*H*O), 2.43 (1H, m, COC*H*Me), 1.72 (1H, m, C*H*Me), 1.42 (1H, m, C*H*aHb), 1.36 (1H, m, CHa*H*b), 1.36 (1H, m, C*H*aHbMe), 1.08 (3H, d, *J* 6.8 Hz, COCH*Me*), 1.05 (1H, m, CHa*H*bMe), 0.89 (3H, d, *J* 7.0 Hz, CH*Me*), 0.88 (3H, t, *J* 7.4 Hz, CH_2*Me*); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 205.5, 44.1, 37.8, 31.9, 29.1, 19.2, 14.1, 11.1; HRMS (ESI): calcd for $C_8H_{17}O$: 129.1279; found 129.1290 $[M+H]^+$.

3.8. (3*S*,4*R*,5*R*,7*R*)-3,5,7-Trimethyl-1-nonen-4-ol 3

A solution of potassium *tert*-butoxide in dry THF (10.5 mL, 10.5 mmol, 2.80 equiv) was cooled to −78 °C, and *trans*-2-butene (1.35 mL, 15.0 mmol, 4.00 equiv) was added, followed by *n*-butyllithium (2.5 M, 4.21 mL, 10.5 mmol, 2.80 equiv). The resulting bright yellow solution was stirred at −78 °C for 2 min and at −45 °C for 20 min. The reaction was re-cooled to −78 °C, and a solution of (−)-*B*-methoxydiisopinocampheylborane (3.79 g, 12.0 mmol, 3.20 equiv) in dry THF was added. The reaction was stirred for 35 min, and $BF_3{\cdot}OEt_2$ (1.47 mL, 12.0 mmol, 3.20 equiv) was added followed by a pre-cooled (−78 °C) solution of (*R*,*R*)-**4** (481 mg, 3.76 mmol, 1.00 equiv) in dry THF (5.00 mL). The resulting solution was stirred at −78 °C for 4 h. The reaction was diluted with saturated aqueous solution of NaCl (40 mL) and extracted with ethyl acetate (3×40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give a dark liquid (3.80 g) that was used in the following step without further purification.

3.9. (3*S*,4*R*,5*R*,7*R*)-4-*O*-(*tert*-Butyl-dimethylsilyl)-3,5,7-trimethyl-1-nonen-4-ol 11

To a stirred solution of homoallylic alcohol **3** (3.80 g) in dry DMF (20.0 mL) were added TBSCl (25.7 g, 41.3 mmol, 2.00 equiv) and imidazole (3.36 g, 49.4 mmol, 2.40 equiv) and the mixture was stirred at room temperature for 24 h. The mixture was diluted with water (30 mL), and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layer was concentrated in vacuo and the residue was purified by column chromatography on silica gel (100% hexane) to give the desired silylether derivative (*S*,*R*,*R*,*R*)-**11** (1.03 g, 92% over two steps) as colorless solid. R_f (hexane) 0.99; $[\alpha]_D$= +13.0 (*c* 9.8, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 5.77 (1H, m, CH_2=C*H*), 4.97 (2H, m, CH_2=CH), 3.36 (1H, m, C*H*OSi), 2.34 (1H, m, =CHC*H*Me), 1.70 (1H, m, OCHC*H*Me), 1.53 (1H, m, CH_2CHMe), 1.37 (2H, m, CH_2), 1.32 (1H, m, C*H*aHbMe), 1.03 (1H, m, CHa*H*bMe), 0.98 (3H, d, *J* 6.7 Hz, =CHCH*Me*), 0.90 (9H, s, Me_3CSi), 0.86 (6H, s, CH*Me*), 0.83 (3H, t, *J* 7.4 Hz, CH_2*Me*), 0.03 (6H, s, Me_2Si); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 142.5, 113.6, 79.5, 42.8, 42.1, 33.9, 31.7, 28.7, 26.2, 19.8, 18.5, 17.6, 15.5, 11.2, −3.7; HRMS (ESI): calcd for $C_{18}H_{39}OSi$: 299.2770; found 299.2750 $[M+H]^+$.

3.10. (2*R*,3*R*,4*R*,6*R*)-3-Hydroxy-2,4,6-trimethyloctanoic acid (2)

To a stirring solution of (*S*,*R*,*R*,*R*)-**11** (500 mg, 1.68 mmol, 1.00 equiv) in dioxane (3.00 mL) and H_2O (3.00 mL) was added 4-methylmorpholine *N*-oxide (295 mg, 2.52 mmol, 1.50 equiv) and osmium tetraoxide (2% in H_2O, 432 μL, 0.034 mmol, 0.02 equiv). After 1 h, $NaIO_4$ (539 mg, 2.52 mmol, 1.50 equiv) was added, and the suspension was stirred at room temperature for 1.5 h. The reaction mixture was cooled to 0 °C, and sodium chlorite (608 mg, 6.72 mmol, 4.00 equiv) and sulfamic acid (652 mg, 6.72 mmol, 4.00 equiv) were added, and the resulting bright yellow mixture was removed from the cold bath and stirred for 2 h. To the mixture was added 5% aqueous HCl (20 mL), and the resulting solution was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with 5% aqueous HCl (20 mL), dried over $MgSO_4$, concentrated, and purified by HPLC (Macherey, Nagel; ET 200/4 Nucleosil 100-5, 5 μ, 250×4.6 mm) with hexane/AcOEt (75:25, with 0.05% TFA) to give pure (*R*,*R*,*R*,*R*)-**2** (t_R=4.0 min, 254 mg, 75%). $[\alpha]_D$= +21.2 (*c* 7.3, chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.49 (1H, t, *J* 5.8 Hz, C*H*OH), 2.74 (1H, quintet, *J* 7.1 Hz, COC*H*Me), 1.74 (1H, m, HOCHC*H*Me), 1.44 (1H, m, C*H*aCHbMe), 1.40 (1H, m, CH_2CHMe), 1.27 (3H, d, *J* 7.1 Hz, COCH*Me*), 1.06 (2H, m, CHaC*H*bMe and C*H*aHb), 1.03 (1H, m, CHa*H*b), 0.97 (3H, d, *J* 6.8 Hz, HOCHCH*Me*), 0.91 (3H, d, *J* 6.2 Hz, CH_2CH*Me*), 0.88 (3H, t, *J*=7.3 Hz, CH_2*Me*); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 180.5, 78.3, 42.3, 37.5, 33.2, 31.5, 27.7, 20.4, 16.9, 14.8, 11.0; HRMS (ESI): calcd for $C_{11}H_{23}O_3$: 203.1647; found 203.1665 $[M+H]^+$.

Data for natural 3-hydroxy-2,4,6-trimethyloctanoic acid (HTMOA): $[\alpha]_D$= +21.8 (*c* 5.4, chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.48 (1H, t, *J* 5.8 Hz, C*H*OH), 2.74 (1H, quintet, *J* 7.1 Hz, COC*H*Me), 1.72 (1H, m, HOCHC*H*Me), 1.46 (1H, m, C*H*aCHbMe), 1.40 (1H, m, CH_2CHMe), 1.29 (3H, d, *J* 7.1 Hz, COCH*Me*), 1.06 (2H, m, CHaC*H*bMe and C*H*aHb), 1.03 (1H, m, CHa*H*b), 0.97 (3H, d, *J* 6.8 Hz, HOCHCH*Me*), 0.91 (3H, d, *J* 6.2 Hz, CH_2CH*Me*), 0.87 (3H, t, *J*=7.3 Hz, CH_2*Me*); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 180.5, 78.3, 42.1, 37.7, 33.4, 31.5, 27.7, 20.4, 16.9, 14.8, 11.0.

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