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

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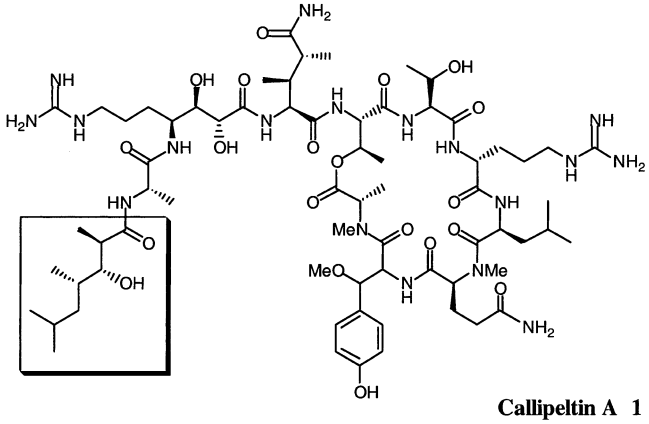
Abstract—An efficient and highly stereocontrolled synthesis of protected (2*R*,3*R*,4*S*)-3-hydroxy-2,4,6-trimethylheptanoic acid, the β-hydroxy acid unit that acylates the N-terminus of callipeltin A, has been devised starting from methyl (2*S*)-2-methyl-3-hydroxypropionate. Comparison of NMR data with the corresponding fragment obtained from the acid hydrolysate of callipeltin A indicates that the stereostructure of the above fragment should be revised.

1. Introduction

The novel cyclodecapeptide callipeltin A **1** and its congeners were isolated in our laboratories from the marine lithistid sponge *Callipelta* sp.[1,2] The intriguing structure of these compounds was characterized by the presence of several non-proteinogenic amino acid units. Callipeltin A **1** was found to protect cells infected by the HIV virus and, recently, it was also found to be a selective and powerful inhibitor of the Na/Ca cardiac exchanger.[3]



Callipeltin A 1

The complex structure of this natural product has already motivated some synthetic efforts, even if no total synthesis has been reported to date. Three syntheses of the unusual amino acid (3*S*,4*R*)-3,4-dimethyl-L-glutamine have been proposed.[4] Recently, a synthesis of (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxyheptanoic acid, a synthetic precursor of the (2*R*,3*R*,4*S*)-4-amino-7-guanidino-2,3-dihydroxyheptanoic acid (AGDHE) residue also appeared in the literature.[5]

En route to a total synthesis of callipeltin A **1**, herein we report an asymmetric synthesis of protected (2*R*,3*R*,4*S*)-3-hydroxy-2,4,6-trimethylheptanoic acid **2**, the β-hydroxy acid linked to the N-terminus of callipeltin A.

2. Results and discussion

Our retrosynthetic analysis of the protected 3-hydroxy-2,4,6-trimethylheptanoic acid **2** is shown in Fig. 1. We envisaged that the isopropyl terminus could be introduced through a Wittig reaction on aldehyde **4**. The C(2)–C(4) stereotriad in **4** would arise from a chiral

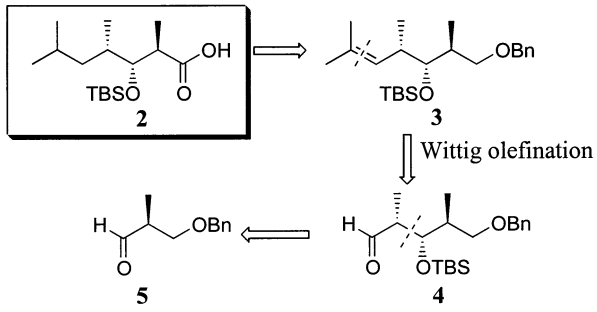


Figure 1.

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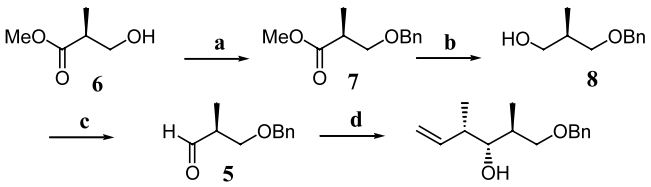
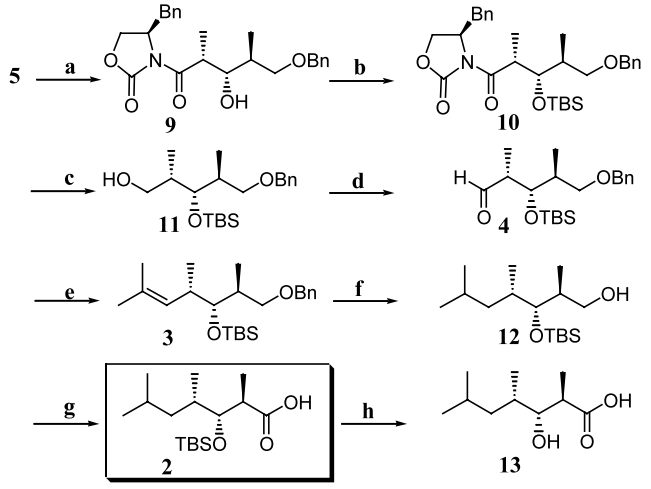


Scheme 1. *Reagents and conditions*: (a) BTCA, TfOH, 0°C to rt, 3 h, 94%; (b) $LiBH_4$, dry MeOH, 2 h, 96%; (c) DMSO, ($COCl_2$), −78°C, 30 min, then **8**, Et_3N, −78°C to rt, 1 h, 97%; (d) *tert*-BuOK, (Z)-2-butene, BuLi, −78 to −45°C, (+)-B-methoxydiisopinocampheylborane, $BF_3{\cdot}OEt_2$, aldehyde **5**, −78°C, 4 h, 70%.

auxiliary-controlled addition (Brown crotylboronation or aldol addition) to the suitable protected aldehyde **5**. This latter could be obtained from commercially available methyl (2*S*)-2-methyl-3-hydroxypropionate **6**.

A first approach towards aldehyde **4** is outlined in Scheme 1. Methyl (2*S*)-2-methyl-3-hydroxy propionate **6** was transformed into aldehyde **5** in a three-step sequence (88% yield for three steps) involving the protection of the primary hydroxy group as its benzyl ether, $LiBH_4$ reduction of the methyl ester function of **7** followed by Swern oxidation[6] of the obtained primary alcohol **8**. Unfortunately, the addition of the chiral boron reagent derived from *cis*-2-butene, and (+)-Ipc_2BOMe to aldehyde **5** under Brown's conditions,[7] proceeded with unsatisfactory 65% diastereoselectivity.

Thus, we turned to the well-established Evans' asymmetric aldol methodology[8] to set up the correct stereochemistry of the three contiguous stereogenic centers (Scheme 2). Treatment of the boron enolate derived



Scheme 2. *Reagents and conditions*: (a) Bu_2BOTf, (*R*)-4-benzyl-3-propionyl-oxazolidinone, −78°C, 1 h, then **5**, −78 to −10°C, 2 h, 81%; (b) 2,6-lutidine, TBSOTf, 0°C to rt, 2 h, 91%; (c) $LiBH_4$, dry MeOH, 0°C, 1 h, 96%; (d) DMSO, ($COCl_2$), −78°C, 30 min, then **11**, Et_3N, −78°C to rt, 1 h, 95%; (e) isopropyltriphenylphosphonium iodide, *n*-BuLi, rt 3 h, 84%; (f) $H_2/Pd(OH)_2$, 3 atm, 2 days, 90%; (g) $NaIO_4$/$RuCl_3{\cdot}H_2O$ (cat.), 84%; (h) MeOH/HCl, 25°C, 3 h, quantitative.

from commercially available (*R*)-4-benzyl-3-propionyl-oxazolidinone with protected aldehyde **5** provided an 81% isolated yield of the diastereomerically pure aldol **9**. Transamidation of aldol **9** followed by treatment of the intermediate Weinreb amide[9] with TBSOTf and 2,6-lutidine yielded a mixture of degradation products. On the basis of these results, aldol adduct **9** was converted to primary alcohol **11** after protection of the secondary alcoholic function as its TBS ether followed by removal of the oxazolidinone auxiliary[10] with $LiBH_4$ in MeOH (87%, two steps). The primary alcohol was oxidized to the corresponding aldehyde under standard Swern conditions,[7] and the unpurified aldehyde **4** was directly subjected to Wittig reaction with isopropylidene–triphenylphosphorane to give the olefin **3**. Hydrogenation of **3** in the presence of Pearlman's catalyst[11] then resulted in simultaneous reduction of the alkene bond and hydrogenolysis of the benzyl protecting group, producing the alcohol **12** which was easily oxidized to the targeted protected β-hydroxy acid **2** using $RuCl_3$–$NaIO_4$.[12]

To confirm the stereostructure of the naturally occurring 3-hydroxy-2,4,6-trimethylheptanoic acid residue, a sample of the acid **2** was deprotected with MeOH/HCl to afford the β-hydroxy acid **13**. Surprisingly, the ^1H NMR spectrum of the compound **13** showed some small but significant differences in the chemical shift values when compared with those reported for the corresponding β-hydroxy acid isolated from the acid hydrolysate of callipeltin A.[1] Therefore, the relative stereochemistry of the 3-hydroxy-2,4,6-trimethylheptanoic acid fragment in callipeltin A **1**, tentatively assigned in our original paper on the basis of vicinal coupling constants and molecular modeling considerations, should be revised. This would require the re-isolation of callipeltin A and further structural studies on the natural 3-hydroxy-2,4,6-trimethylheptanoic acid fragment.

3. Conclusion

In summary, we have developed an efficient, highly stereoselective synthesis (10 steps, 38% overall yield) of protected (2*R*,3*R*,4*S*)-3-hydroxy-2,4,6-trimethylheptanoic acid **2** starting from commercially available methyl (2*S*)-2-methyl-3-hydroxypropionate. Small differences in the ^1H NMR data of the synthetic and natural fragments lead us to conclude that the stereochemistry of the deprotected synthetic derivative **13** differs from the corresponding residue in callipeltin A **1** at one or more stereogenic centers. Further studies devoted to the determination of the actual stereochemistry of the 3-hydroxy-2,4,6-trimethylheptanoic acid fragment in callipeltin A are currently in progress in our laboratory.

4. Experimental

NMR spectra were recorded in $CDCl_3$ ($\delta_H = 7.26$ and $\delta_C = 77.0$ ppm) on a Bruker 500 MHz spectrometer and

chemical shifts are reported in ppm. EI MS spectra were performed on a VG Prospec (Fisons) mass spectrometer. IR spectroscopy was performed on a IFS 48 Bruker instrument. Optical rotations were measured with a Perkin–Elmer 141 polarimeter operating at 589 nm. Methyl (2*S*)-(+)-3-hydroxy-2-methylpropionate was purchased from Fluka. Solvents and reagents were used as supplied from commercial sources with the following exceptions. Tetrahydrofuran, toluene, dichloromethane and triethylamine were distilled from calcium hydride immediately prior to use. All reaction 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.

4.1. Methyl (2*S*)-3-benzyloxy-2-methylpropionate 7

A solution of methyl (2*S*)-(+)-3-hydroxy-2-methylpropionate **6** (2.0 g, 16.9 mmol) in CH_2Cl_2/cyclohexane (1:2, 25 mL) was cooled to 0°C and treated with benzyl 2,2,2-trichloroacetimidate (5.1 g, 20.3 mmol) and triflic acid (150 μL, 1.7 mmol). The reaction mixture was allowed to stir at room temperature for 3 h and the precipitated trichloroacetamide was filtered through a small pad of silica gel. The filtrate was washed with saturated $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. Silica gel chromatography (*n*-hexane:ethyl acetate, 99:1) afforded the benzyl ether **7** as a colorless oil (3.3 g, 94%). IR (KBr): 2999, 1725, 1200, 900, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.18 (d, $J=7.2$ Hz, 3H, CH_3), 2.79 (m, 1H, C2-H), 3.50 (dd, $J=9.4$, 6.0 Hz, 1H, C3-Ha), 3.67 (t, $J=9.4$, Hz, 1H, C3-Hb), 3.69 (s, 3H, OCH_3), 4.52 (s, 2H, benzylic CH_2), 7.26–7.35 (m, 5H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 40.1, 51.7, 72.0, 73.1, 127.5, 128.3, 138.2, 175.2; EI MS: m/z 208 (M^+); $[\alpha]_D$ +10.2 (*c* 3, $CHCl_3$).

4.2. (2*R*)-3-Benzyloxy-2-methyl-1-propanol 8

Dry methanol (1.4 mL, 43.2 mmol) and $LiBH_4$ (21.6 mL, 2 M in THF, 43.2 mmol) were added to a solution of **7** (3.0 g, 14.4 mmol) in dry THF under an argon atmosphere and the resulting mixture was stirred for 2 h. The mixture was quenched by addition of NaOH (1 M, 30 mL) and then allowed to warm to room temperature. Ethyl acetate was added and the separated aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic phases were washed with water, dried (Na_2SO_4) and concentrated. Silica gel chromatography (*n*-hexane:ethyl acetate 85:15) afforded the alcohol **8** as a colorless oil (2.5 g, 96%). IR (KBr): 3300, 3068, 1200, 900, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.89 (d, $J=7.7$ Hz, 3H, CH_3), 2.04 (m, 1H, C2-H), 3.49 (t, $J=8.6$, Hz, 1H, C3-Ha), 3.54 (dd, $J=8.6$, 5.0 Hz, 1H, C3-Hb) 3.60 (m, 2H, C1-H), 4.52 (s, 2H, benzylic CH_2), 7.26–7.35 (m, 5H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.4, 35.5, 67.6, 73.4, 75.2, 127.5, 128.5, 138.0; EI MS: m/z 180 (M^+); $[\alpha]_D$ +11.3 (*c* 4.9, $CHCl_3$).

4.3. (2*S*)-3-Benzyloxy-2-methylpropanal 5

DMSO (4.1 mL, 53.2 mmol) was added dropwise over 15 min to a solution of oxalyl chloride (2.3 mL, 26.6 mmol) in dry dichloromethane (50 mL) at −78°C under argon atmosphere. After 30 min a solution of the alcohol **8** (2.4 g, 13.3 mmol) in dry CH_2Cl_2 was added via cannula and the mixture was stirred at −78°C for 1 h. Et_3N (9.3 mL, 66.5 mmol) was added dropwise and the mixture was allowed to warm to room temperature. The reaction was quenched by addition of aqueous $NaHSO_4$ (1 M, 50 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with $NaHSO_4$, water, saturated aqueous $NaHCO_3$ and brine. The organic phase was then dried and concentrated to give the corresponding aldehyde **5** (2.3 g, 97%) as a colorless oil which was used without any further purification.

4.4. (4*R*,2′*R*,3′*S*,4′*S*)-4-Benzyl-3-(5′-benzyloxy-3′-hydroxy-2′,4′-dimethylpentanoyl)-2-oxazolidinone 9

Bu_2BOTf (15.5 mL, 1 M in CH_2Cl_2, 15.5 mmol) and Et_3N (2.3 mL, 16.8 mmol) were added to a solution of (*R*)-4-benzyl-3-propionyl-oxazolidinone (3.3 g, 14.2 mmol) in dry dichloromethane (70 mL) at −78°C under argon and the resulting pale yellow solution was stirred for 1 h at −78°C and then at 0°C for 30 min before re-cooling to −78°C. A solution of the aldehyde **5** (2.3 g, 12.9 mmol) in dry CH_2Cl_2 was cannulated to the solution which was stirred at −78°C for 1 h and then warmed to −10°C, stirred for 1 h and then quenched with pH 7 potassium phosphate monobasic-sodium hydroxide buffer (14 mL). A solution of 30% H_2O_2 in MeOH (1:2, 32 mL) was added to the mixture that was stirred overnight at room temperature and concentrated. The residue was diluted with CH_2Cl_2 and the resulting layers separated. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$, water and brine. The organic phase was then dried (Na_2SO_4), concentrated and chromatographed on silica gel (*n*-hexane:ethyl acetate, 8:2) to give **9** as a colorless oil (4.3 g, 81%). IR (KBr): 3540, 3000, 1780, 1700, 1200, 900, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.96 (d, $J=6.9$ Hz, 3H, CH_3), 1.26 (d, $J=7.2$ Hz, 3H, CH_3), 1.98 (m, 1H, C4′-H), 2.76 (dd, $J=13.2$, 9.5 Hz, 1H, benzylic CH_2), 3.32 (dd, $J=13.2$, 2.9 Hz, 1H, benzylic CH_2), 3.60 (dd, $J=8.8$, 4.4 Hz, 1H, C5′-Ha), 3.88 (dd, $J=8.8$, 2.9 Hz, 1H, C5′-Hb), 3.94 (m, 2H, C2′-H, C3′-H), 4.16 (bs, 2H, C5-H), 4.51 (s, 2H, benzylic CH_2O), 4.66 (m, 1H, C4-H), 7.20–7.35 (m, 10H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.7, 13.6, 36.0, 37.7, 40.6, 55.5, 66.1, 73.5, 74.8, 75.2, 127.3, 127.5, 128.4, 128.9, 129.4, 135.3, 137.8, 153.1, 176.2; EI MS: m/z 411 (M^+); $[\alpha]_D$ −21.9 (*c* 5.6, $CHCl_3$).

4.5. (4*R*,2′*R*,3′*S*,4′*S*)-4-Benzyl-3-(5′-benzyloxy-3′-(*tert*-butyldimethylsilyloxy)-2′,4′-dimethyl-pentanoyl)-2-oxazolidinone 10

2,6-Lutidine (2.9 mL, 25.5 mmol) and TBSOTf (3.9 mL, 17 mmol) were added sequentially to a solution of

the alcohol **9** (3.5 g, 8.5 mmol) in dry CH_2Cl_2 at 0°C under an argon atmosphere. The mixture was allowed to warm at room temperature where stirring was continued for 2 h. Saturated $NaHCO_3$ was added and the organic phase was washed with water, dried ($MgSO_4$) and then concentrated in vacuo. Purification by column chromatography on silica gel using *n*-hexane:EtOAc (98:2) as eluent gave the silyl ether **10** as a colorless oil (4.0 g, 91%). IR (KBr): 3540, 3000, 1780, 1700, 1200, 1100, 900, 800, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 6H, Si-CH_3), 0.90 (s, 9H, Si-C(CH_3)$_3$), 1.02 (d, $J=7.0$ Hz, 3H, CH_3), 1.24 (d, $J=7.2$ Hz, 3H, CH_3), 1.98 (m, 1H, C4′-H), 2.70 (dd, $J=13.2$, 9.6 Hz, 1H, benzylic CH_2), 3.20 (m, 2H, benzylic CH_2, C5′-Ha), 3.57 (dd, $J=8.8$, 5.9 Hz, 1H, C5′-Hb), 3.69 (t, $J=8.8$, Hz, 1H, C5-Ha), 3.99 (m, 2H, C2′-H, C5-Hb), 4.04 (d, $J=7.3$ Hz, C3′-H), 4.42 (m, 1H, C4-H), 7.20–7.35 (m, 10H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.0, 14.7, 18.3, 26.0, 37.6, 38.9, 41.5, 55.4, 65.7, 72.0, 72.9, 75.2, 127.3, 128.3, 128.9, 129.4, 135.4, 138.4, 152.8, 176.1; EI MS: m/z 525 (M^+); $[\alpha]_D$ −13.0 (c 1.2, $CHCl_3$).

4.6. (2*S*,3*R*,4S)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-1-pentanol 11

Dry methanol (585 mL, 18.3 mmol) and $LiBH_4$ (9.1 mL, 2 M in THF, 18.3 mmol) were added to a solution of the amide **10** (3.2 g, 6.1 mmol) in dry THF at 0°C under argon and the resulting mixture was stirred for 1 h at 0°C. The mixture was quenched by addition of NaOH (1 M, 30 mL) and then allowed to warm to room temperature. Ethyl acetate was added and the separated aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic phases were washed with water, dried (Na_2SO_4) and concentrated. Purification by silica gel (*n*-hexane:EtOAc, 85:15) gave the alcohol **11** as a colorless oil (2.0 g, 96%). IR (KBr): 3540, 3000, 1200, 1100, 900, 800, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.04 (s, 3H, Si-CH_3), 0.07 (s, 3H, Si-CH_3), 0.87 (d, $J=7.0$ Hz, 3H, CH_3), 0.90 (s, 9H, Si-C(CH_3)$_3$), 0.98 (d, $J=7.0$ Hz, 3H, CH_3), 1.88 (m, 1H, C2-H), 2.02 (m, 1H, C4-H), 3.31 (t, $J=8.8$ Hz, 1H, C5-Ha), 3.47 (dd, $J=10.3$, 5.8 Hz, 1H, C1-Ha), 3.54 (dd, $J=8.8$, 1.0 Hz., 1H, C5-Hb), 3.57 (dd, $J=10.3$, 5.1 Hz, 1H, C1-Ha), 3.76 (dd, $J=5.5$, 2.9 Hz, 1H, C3-H), 4.51 (s, 2H, benzylic CH_2), 7.32 (m, 5H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.3, 11.7, 15.0, 26.0, 37.6, 38.9, 66.1, 72.9, 73.1, 74.7, 127.5, 127.6, 128.3, 138.5; EI MS: m/z 352 (M^+); $[\alpha]_D$ −1.2 (c 3.5, $CHCl_3$).

4.7. (2*R*,3*S*,4*S*)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-pentanal 4

DMSO (1.7 mL, 21.6 mmol) was added dropwise over 15 min to a solution of oxalyl chloride (5.4 mL, 2 M in CH_2Cl_2, 10.8 mmol) in dry dichloromethane (25 mL) at −78°C under an argon atmosphere. After 30 min a solution of the alcohol **11** (1.9 g, 5.4 mmol) in dry CH_2Cl_2 was added via cannula and the mixture was stirred at −78°C for 1.5 h. Et_3N (3.7 mL, 27.5 mmol) was added dropwise and the mixture was allowed to warm to room temperature. The reaction was quenched by addition of aqueous $NaHSO_4$ (1 M, 25 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with $NaHSO_4$, water, saturated aqueous $NaHCO_3$, and brine. The organic phase was then dried (Na_2SO_4), concentrated to give the corresponding aldehyde **4** (1.8 g, 95%) as a colorless oil which was used without any further purification.

4.8. (2*S*,3*R*,4*S*)-1-*O*-Benzyl-3-(*tert*-butyldimethylsilyloxy)-2,4,6-trimethyl-5-hepten-1,3-diol 3

n-BuLi (15.9 mL, 1.6 M in hexane, 25.5 mmol) was added dropwise to a suspension of isopropyltriphenylphosphonium iodide (11.2 g, 26 mmol) in dry THF (70 mL) at room temperature. The resulting red solution was stirred at room temperature for 30 min. A solution of the aldehyde **4** (1.8 g, 5.1 mmol) in dry THF (10 mL) was introduced via cannula. The solution immediately became yellow. After 2 h the reaction was diluted with ethyl acetate and washed with saturated $NaHCO_3$, water, dried (Na_2SO_4) and concentrated. The residue was chromatographed on SiO_2 eluting with 995:5 hexane:ethyl acetate to afford **3** (1.6 g, 84%). IR (KBr): 3000, 1660, 1200, 1100, 900, 800, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.07 (s, 6H, Si-(CH_3)$_2$), 0.93 (s, 9H, Si-C(CH_3)$_3$), 0.94 (d, $J=7.1$ Hz, 3H, CH_3), 1.02 (d, $J=7.0$ Hz, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 2.05 (m, 1H, C2-H), 2.56 (m, 1H, C4-H), 3.29 (t, $J=8.8$ Hz, 1H, C1-Ha), 3.46 (t, $J=5.1$ Hz, 1H, C3-H), 3.57 (dd, $J=8.8$, 5.1 Hz, 1H, C1-Hb), 4.50 (s, 2H, benzylic CH_2), 4.98 (d, $J=9.7$ Hz, C5-H), 7.34–7.37 (m, 5H, aromatic); ^{13}C NMR (125 MHz, $CDCl_3$): δ −3.9, 14.8, 17.1, 17.9, 18.4, 25.8, 26.2, 35.9, 38.5, 72.9, 78.5, 127.9, 127.3, 128.2, 128.5, 128.7, 129.4, 129.7, 133.7, 133.8, 138.9; EI MS: m/z 376 (M^+); $[\alpha]_D$ −5.9 (c 2.6, $CHCl_3$).

4.9. (2*S*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethylheptan-1-ol 12

A solution of **3** (950 mg, 2.5 mmol) in ethanol was hydrogenated in the presence of a Pearlman's catalyst (100 mg) for 2 days in a Parr apparatus (3 atm). The mixture was filtered through Celite and the filtrate was concentrated in vacuo. Purification by column chromatography on silica gel using *n*-hexane:EtOAc (97:3) gave **12** as a colorless oil (654 mg, 90%); IR (KBr): 1200, 1100, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.07 (s, 3H, Si-CH_3), 0.10 (s, 3H, Si-CH_3), 0.83 (d, $J=7.0$ Hz, 3H, CH_3), 0.86 (d, $J=7.3$ Hz, 3H, CH_3), 0.89 (d, $J=6.9$ Hz, 3H, CH_3), 0.91 (s, 9H, Si-C(CH_3)$_3$), 0.94 (d, $J=7.0$ Hz, 3H, CH_3), 1.09 (m, 1H, C5-Ha), 1.21 (m, 1H, C5-Hb), 1.59 (m, 1H, C6-H), 1.69 (m, 1H, C4-H), 1.85 (m, 1H, C2-H), 3.46 (t, $J=5.1$ Hz, 1H, C3-H), 3.59 (t, $J=6.0$ Hz, 2H, C1-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.1, −4.0, 15.0, 16.2, 18.2, 21.7, 23.8, 25.3, 26.1, 35.5, 37.9, 42.6, 66.1, 81.1; EI MS: m/z 288 (M^+); $[\alpha]_D$ −16.6 (c 1, $CHCl_3$).

4.10. (2*R*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethyl-heptanoic acid 2

To a stirred solution of **12** (620 mg, 2.1 mmol) in CCl_4 (4 mL), CH_3CN (4 mL) and water (6 mL) were added

sodium *meta*-periodate (1.8 g, 8.6 mmol) and $RuCl_3 \cdot H_2O$ (10.8 mg, 0.04 mmol) sequentially. The mixture was stirred at 25°C for 2 h. Diethyl ether (20 mL) was added and the stirring was continued for 20 min to precipitate black RuO_2. The reaction mixture was dried and filtered through Celite and the solid residue was washed with ether. The combined organic phases were concentrated and chromatographed (*n*-hexane:EtOAc, 9:1) to give the carboxylic acid **2** (546 mg, 84%); IR (KBr): 1725, 1200, 1100, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.05 (s, 3H, Si-CH_3), 0.08 (s, 3H, Si-CH_3), 0.83 (d, $J=6.9$ Hz, 3H, CH_3), 0.85 (d, $J=7.0$ Hz, 3H, CH_3), 0.87 (d, $J=7.5$ Hz, 3H, CH_3), 0.89 (s, 9H, Si-C(CH_3)$_3$), 1.09 (m, 1H, C5-Ha), 1.16 (d, $J=7.0$ Hz, 3H, CH_3), 1.20 (m, 1H, C5-Hb), 1.61 (m, 1H, C6-H), 1.71 (m, 1H, C4-H), 2.65 (m, 1H, C2-H), 3.78 (dd, $J=6.6$, 2.9 Hz, 1H, C3-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.5, −4.0, 14.2, 14.7, 18.3, 21.7, 23.5, 25.1, 26.0, 33.9, 42.3, 44.2, 77.9, 180.6; EI MS (relative intensity): m/z 245 (M^+–54, 100), 229 (20), 217 (24), 131 (45); HREI MS: for $C_{12}H_{25}SiO_3$ found 245.1577, calcd. 245.1573; $[\alpha]_D$ –12.4 (*c* 2.3, $CHCl_3$).

4.11. (2*R*,3*R*,4*S*)-3-Hydroxy-2,4,6-trimethylheptanoic acid 13

A solution of HCl in MeOH (2N, 5 mL) was added to a solution of **2** (35 mg, 0.12 mmol) in methanol (1 mL) at room temperature. The reaction was stirred for 3 h and Ag_2CO_3 was added. The mixture was treated with a stream of N_2 to eliminate CO_2, and concentrated in vacuo. The residue was purified by silica gel chromatography (chloroform:methanol 98:2) to afford **13** as a colorless oil (21.7 mg, quantitative). IR (KBr): 3400, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.85 (d, $J=6.6$ Hz, 6H, CH_3), 0.89 (d, $J=6.5$ Hz, 3H, CH_3), 1.15 (m, 1H, C5-Ha), 1.17 (d, $J=7.0$ Hz, 3H, CH_3), 1.24 (m, 1H, C5-Hb), 1.66 (m, 2H, C6-H, C4-H), 2.40 (d, $J=5.9$ Hz, 1H, OH), 2.65 (quint, $J=7.7$ Hz, 1H, C2-H), 3.56 (ddd, $J=7.7$, 5.9, 2.9 Hz, 1H, C3-H); EI MS: m/z 188 (M^+); $[\alpha]_D$ −20 (*c* 0.1, $CHCl_3$).

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