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TETRAHEDRON: *ASYMMETRY*

Progress towards the total synthesis of callipeltin A. Asymmetric synthesis of (2*R*,3*R*,4*S*)-3-hydroxy-2,4,6-trimethylheptanoic acid

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Abstract—A silyl derivative of (2*R*,3*R*,4*S*)-3-hydroxy-2,4,6-trimethylheptanoic acid, a moiety present in the cyclic depsipeptide callipeltin A, was successfully synthesized from L-valine in nine steps using the Heathcock variant of the Evans aldol reaction.

1. Introduction

Cyclic depsipeptides have emerged as a very important class of bioactive compounds isolated from marine natural products.[1] In 1996, Zampella et al. reported the isolation of callipeltin A, a cyclic depsipeptide with antiviral and antifungal properties isolated from a shallow water sponge of the genus *Callipelta*, collected in the waters off New Caledonia (Fig. 1).[2] More recently, Luciani and co-workers have shown that callipeltin A is a selective and powerful inhibitor of the cardiac sodium/calcium exchanger and is therefore of great interest as a regulator of myocardial contractility.[3] En route to a total synthesis of callipeltin A, we have reported the synthesis of (3*S*,4*R*)-3,4-dimethylglutamine through an asymmetric Michael addition using a camphorsultam auxiliary.[4] More recently two other groups have achieved the synthesis of this amino acid residue.[5,6] The synthesis of fully protected (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxyheptanoic acid has also been reported recently.[7]

We now disclose a stereoselective synthesis of the silyl ether of (2*R*,3*R*,4*S*)-3-hydroxy-2,4,6-trimethylheptanoic acid **1**. The synthesis involves the use of oxazolidinone chemistry[8] for both stereoselective alkylation and aldol

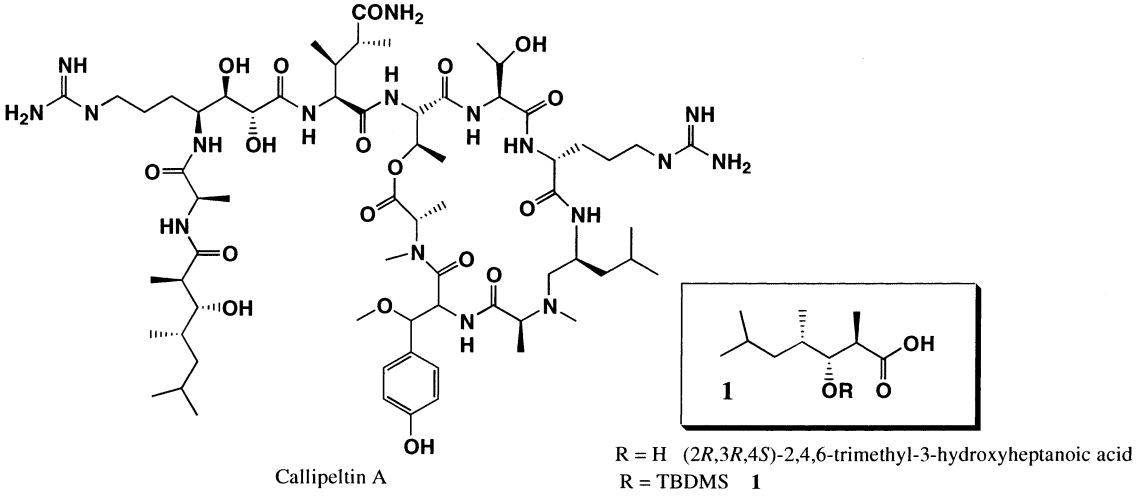

Figure 1. Callipeltin A and acid **1**.

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condensation reactions.[9] The retrosynthetic analysis is shown in Fig. 2.

2. Results and discussion

The chiral auxiliary employed for the asymmetric synthesis of (4*S*)-4-isopropyl-3-[(2′*S*)-2′,4′-dimethylvaleryl)]-2-oxazolidinone **6** was the Evans oxazolidinone **3** (Scheme 1). Evans and co-workers reported asymmetric alkylation reactions of chiral imide enolates as a practical approach to the enantioselective synthesis of α-substituted carboxylic acid derivatives.[10] Oxazolidinone **3** was prepared from L-valine in two steps in 62% overall yield.[11,12] *N*-Acylation using *n*-BuLi and 4-methylvaleric acid activated with pivaloyl chloride, provided carboximide **5** in 79% yield. Methylation at the 2′-position was carried out by treatment with LDA at −78°C, followed by alkylation with iodomethane to afford **6** in 65% yield following crystallization from hexane. The absolute configuration of **6** was established by X-ray crystallographic analysis (Fig. 3).

Conversion of the carboximide functional group to the desired aldehyde moiety was achieved by reduction[11] with $LiAlH_4$ followed by Swern oxidation (Scheme 2).[13,14] Attempts to obtain aldehyde **8** by other oxidation methods (Dess–Martin periodinane,[15] Collins oxidation[16]) failed. The unstable aldehyde was used without further purification in the aldol reaction. Treatment with Et_2AlCl in CH_2Cl_2 at −78°C, followed by addition of the boron enolate of carboximide **4** produced the *anti* aldol product **9** in 21% yield over two steps following crystallization. Heathcock et al. reported that the *anti* aldol reaction results from the open transition state B shown in Fig. 4, a transition state which is favored by sterically demanding Lewis acids such as Et_2AlCl.[9] The structure and stereochemistry of **9** were confirmed by X-ray crystallography (Fig. 5).

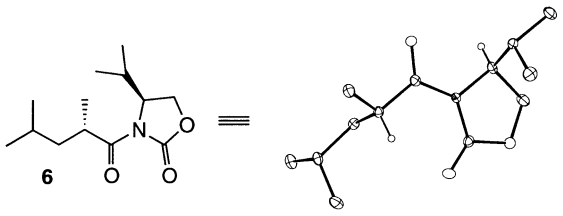


Figure 3. ORTEP drawing of (4*S*)-4-isopropyl-3-[(2′*S*)-2′,4′-dimethylvaleryl)]-2-oxazolidinone **6**.

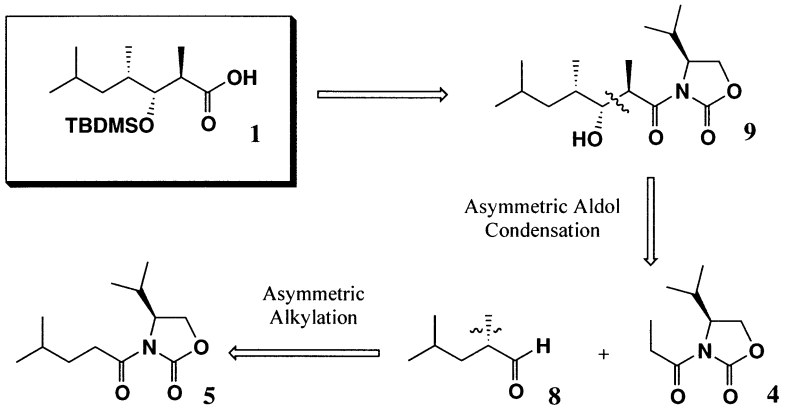
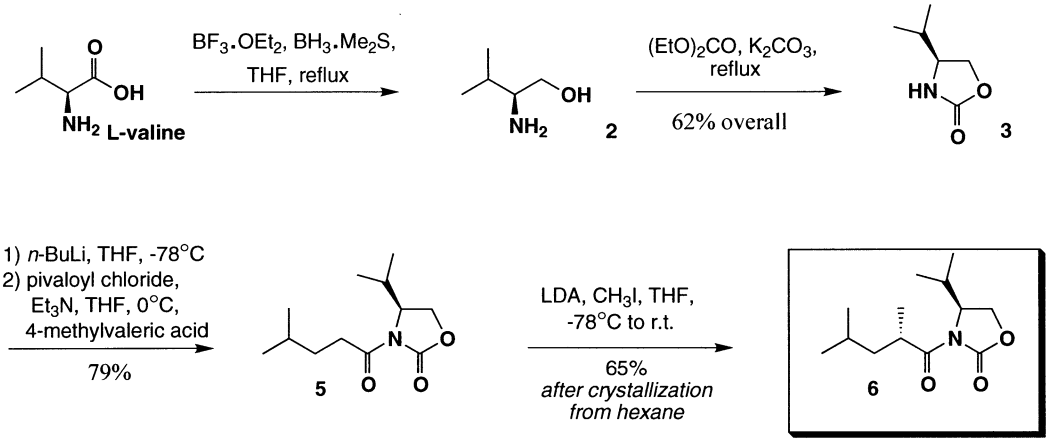
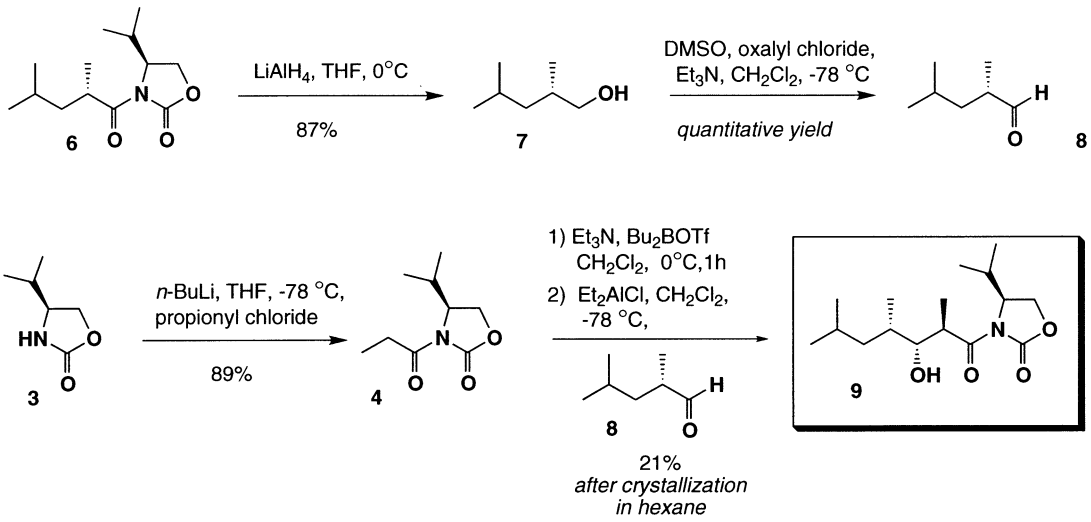


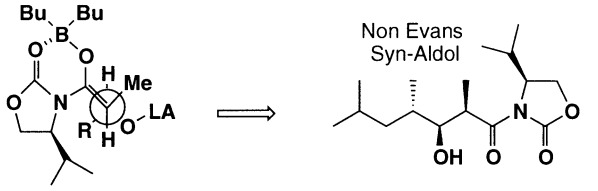
Figure 2. Retrosynthetic analysis of (2*S*,3*R*,4*S*)-trimethyl-3-*tert*-butyldimethylsiloxyheptanoic acid **1**.



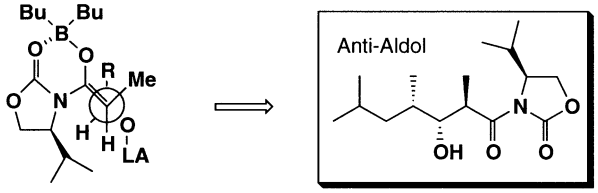
Scheme 1.



Scheme 2.



Transition state A : favored for small Lewis acids ($SnCl_4$ and $TiCl_4$)



Transition state B : favored for large Lewis acids (Et_2AlCl)

Figure 4. Heathcock's transition state models of aldol reactions.

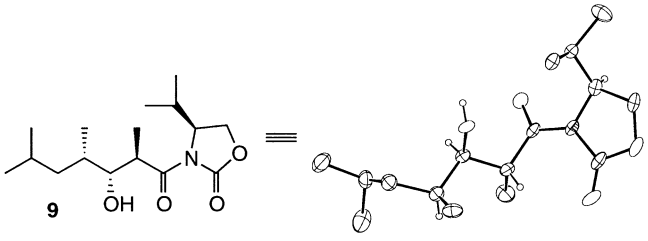


Figure 5. ORTEP drawing of (4*S*)-4-isopropyl-3-[(2′*R*,3′*S*, 4′*S*)-2′,4′,6′-trimethyl-3′-hydroxyheptyl)]-2-oxazolidinone **9**.

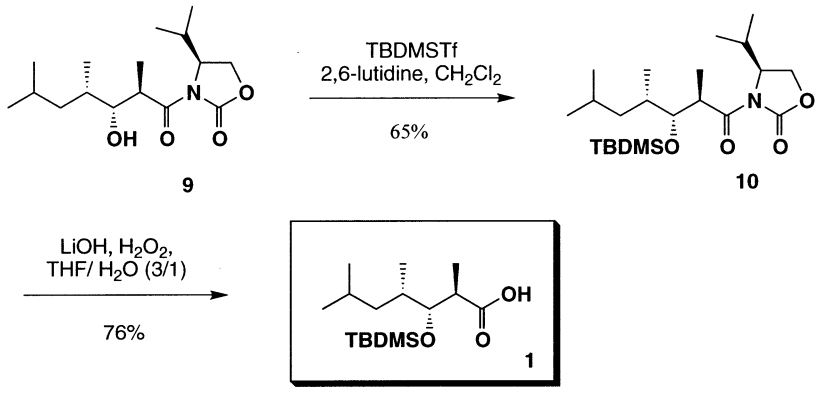
In order to utilize **1** in the total synthesis of callipeltin A, acid **9** was protected as its silyl ether **10** using *tert*-butyldimethylsilyl triflate[17] and 2,6-lutidine in CH_2Cl_2. Initial attempts to introduce the silyl group with *tert*-butyldimethylsilyl chloride and imidazole failed. The removal of the chiral auxiliary was achieved with lithium hydroxide and 30% hydrogen peroxide in a solution of THF/H_2O (3/1) to afford the target **1** in 76% yield (Scheme 3).

3. Conclusion

An efficient synthesis of protected (2*R*,3*R*,4*S*)-3-hydroxy-2,4,6-trimethylheptanoic acid from L-valine has been accomplished in nine steps. The approach is flexible and applicable to other analogues, which may be produced by the use of a wide range of aldehydes in the aldol condensation.

4. Experimental

All manipulations were conducted under an inert atmosphere (argon or nitrogen). All solvents were reagent grade. Tetrahydrofuran (THF) was distilled from sodium and benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride (CaH_2). Organic acids and bases were reagent grade. Triethylamine and 2,6-lutidine were distilled from calcium hydride. All other reagents were commercial compounds of the highest purity available. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel (60 F-254, plates 0.25 mm). Detection was accomplished either with phosphomolybdic acid (7% in ethanol) or potassium permanganate. Flash column chromatography was carried out on Merck silica gel 60 particle size (0.040–0.063 mm). Melting points (mp) were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. Proton and carbon magnetic resonance spectra (^1H, ^{13}C NMR) were recorded on a Bruker AM-500 Fourier transform spectrometer, and chemical shifts are expressed in parts per million relative to tetramethylsilane (TMS, 0 ppm) or $CHCl_3$ as an internal reference (7.28 ppm for ^1H and 77.0 ppm for ^{13}C). Infrared spectra (IR) were obtained on Perkin–Elmer Model 1600 Series FTIR spectrometer. Absorptions are reported in wavenumbers (cm^{-1}) and the spectra were calibrated against the 1601 cm^{-1}



Scheme 3.

band of a polystyrene film. Optical rotations were recorded on a Perkin–Elmer Model 341 polarimeter at the sodium D line. High-resolution mass spectra (HRMS) were obtained on either a VG 70–70HS [a high-resolution double focusing mass spectrometer using ammonia chemical ionization (CI) or electron impact (EI)] or a ZAB-E [using fast atom bombardment (FAB), CI, or EI].

4.1. (4*S*)-4-Isopropyl-2-oxazolidinone 3

Boron trifluoride diethyl etherate (22 mL, 0.17 mol) was added over a 30 min period to a solution of L-valine (20 g, 0.17 mol) in THF (110 mL). The mixture was heated under reflux for 1 h. The reaction temperature was adjusted to below the reflux point, and borane–dimethyl sulfide complex (17.80 mL, 0.19 mol) was added dropwise over 2 h. During the addition, hydrogen evolved, and methyl sulfide was allowed to distill as it was generated. The solution was then refluxed for 6 h and cooled to ambient temperature. The remaining borane was quenched by careful addition of 15 mL of 1:1 THF/water. To the solution was added 5 M aqueous NaOH solution (90 mL). The mixture was heated at reflux for 12 h. The remaining THF was removed in vacuo, and the resulting slurry was extracted with CH_2Cl_2 (5×20 mL). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo to give **2** as oil (12.3 g, 70%).

(*S*)-Valinol **2** (12.3 g, 0.12 mmol), diethyl carbonate (28.8 mL, 0.24 mol), and potassium carbonate (1.64 g, 0.012 mmol) were placed into a flask equipped with a Dean–Stark apparatus. The magnetically stirred mixture was heated at 145°C until 14 mL (11 g, 0.24 mmol) of ethanol was collected. The resultant mixture was cooled to room temperature and diluted with diethyl ether (100 mL), and the resulting suspension was filtered through a 2 cm pad of Celite to remove the potassium carbonate. The ethereal solution was concentrated to a volume of 100 mL and slowly cooled to 0°C, and the product was allowed to crystallize. Concentration of the mother liquors provided two additional crops of crystals. The total yield of oxazolidinone **3**, obtained as white needles, was 9.59 g (62%, two steps). R_f 0.52 {ethyl acetate/hexane (5/5)}; mp 70°C (lit.[12] mp 69–70°C, lit,[8,18] mp 71–72°C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, 3H, J=6.74 Hz), 0.97 (d, 3H, J=6.67 Hz), 1.73 (m, 1H), 3.62 (m, 1H), 4.10 (m, 1H), 4.44 (m, 1H), 6.72 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.59, 17.93, 32.64, 58.36, 68.56, 160.40; IR ν_{max} (KBr, $CHCl_3$) 3261, 2960, 1750, 1479, 1405, 1351, 1327, 1246, 1090, 936, 900, 770, 715 cm^{-1}; HRMS m/z calcd for $C_6H_{11}NO_2$ (M+H) 130.0868, found 130.0873; [α]= +13.3 ($CHCl_3$, c 6.8) lit.[8] +14.8 ($CHCl_3$, c 7) and lit.[18] +16.8 ($CHCl_3$, c 17.5).

4.2. (4*S*)-4-Isopropyl-3-propionyl-2-oxazolidinone 4

A solution of n-BuLi in hexanes (1.6 M, 10.7 mL, 17.12 mmol) was added dropwise over 3 min to a stirred solution of **3** (2 g, 15.5 mmol) in anhydrous THF (30 mL) at −78°C. The mixture was stirred at this temperature for 20 min and propionyl chloride (1.48 mL, 17 mmol) was then added dropwise over 2 min. The mixture was stirred for 30 min and then quenched with saturated aqueous NH_4Cl solution (100 mL). The solution was extracted with ethyl acetate (100 mL) and the organic phase was washed with brine. The dried solution (Na_2SO_4) was concentrated in vacuo and the residue was then purified using flash chromatography (10% ethyl acetate in hexanes) to provide **4** as a colorless oil (2.38 g, 83%). R_f 0.27 {ethyl acetate/hexane (2/8)}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, 3H, J=7 Hz), 0.93 (d, 3H, J=7 Hz), 1.18 (td, 3H), 2.39 (m, 1H), 2.97 (m, 2H), 4.22 (m, 1H), 4.28 (m, 1H), 4.44 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.42, 14.65, 17.93, 28.39, 29.11, 58.40, 63.37, 154.10, 174.04; IR ν_{max} (KBr, $CHCl_3$) 2965, 2941, 2878, 2350, 2338, 1787, 1702, 1487, 1464, 1388, 1375, 1301, 1247, 1207, 1143, 1120, 1072, 1026, 982, 947, 806, 773, 758, 699 cm^{-1}; HRMS m/z calcd for $C_9H_{15}NO_3$ (M+Na) 208.105, found 208.095; [α]=+92 (CH_2Cl_2, c 1.4) lit.[8] +96.8 (CH_2Cl_2, c 8.7) and lit.[18] +94 (CH_2Cl_2, c 1.75)].

4.3. (4*S*)-4-Isopropyl-3-(4′-methylvaleryl)-2-oxazolidinone 5

A solution of n-BuLi in hexanes (2.5 M, 11.2 mL, 28 mmol) was added dropwise to a stirred solution of **3** (3 g, 23.2 mmol) in anhydrous THF (100 mL) at −78°C. The mixture was stirred at this temperature for 30 min.

In a separate flask containing 4-methylvaleric acid (3.53 mL, 27.9 mmol) and THF (100 mL) at 0°C was added triethylamine (5.51 mL, 39.6 mmol) and pivaloyl chloride (3.73 mL, 30.3 mmol). After stirring for 30 min, the lithio-(4*S*)-4-isopropyl-2-oxazolidinone was added. The mixture was warmed to room temperature over a 2 h period. The solution was extracted with EtOAc and the organic extract was washed with saturated $NaHCO_3$, saturated NH_4Cl solution, and brine. The dried solution (Na_2SO_4) was concentrated in vacuo and the residue was then purified using flash chromatography (10% ethyl acetate in hexanes) to provide **5** (3.69 g, 70%) as colorless oil. R_f 0.28 {ethyl acetate/hexane (2/8)}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, 3H, $J=7$ Hz), 0.91 (d, 3H, $J=7$ Hz), 0.925 (d, 3H, $J=6.5$ Hz), 0.926 (d, 3H, $J=6.5$ Hz), 1.56 (m, 2H), 1.60 (m, 1H), 2.35 (m, 1H), 2.88 (m, 1H), 2.97 (m, 1H), 4.20 (m, 1H), 4.25 (m, 1H), 4.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.6, 17.8, 22.2 (2 overlapping carbons), 27.6, 28.3, 33.2, 33.5, 58.3, 63.2, 153.9, 173.5; IR ν_{max} (KBr, $CHCl_3$) 2959, 2935, 2872, 2360, 1782, 1702, 1467, 1388, 1340, 1301, 1281, 1204, 1144, 1132, 1120, 1092, 1061, 1019, 971, 774, 704, 634 cm^{-1}; HRMS *m/z* calcd for $C_{12}H_{21}NO_3$ (M+Na) 250.1521, found 250.1407; $[\alpha]=+71.2$ ($CHCl_3$, *c* 1).

4.4. (4*S*)-4-Isopropyl-3-[(2′*S*)-2′,4′-dimethylvaleryl)]-2-oxazolidinone 6

A solution of diisopropylamine (3.42 mL, 24.4 mmol) in THF (30 mL) was cooled to −30°C and *n*-BuLi in hexanes (2.5 M, 8.45 mL, 21.12 mmol) was added. After stirring the mixture for 45 min, a solution of **5** (3.69 g, 16.25 mmol) in THF (20 mL) was added at −78°C. The mixture was stirred at −78°C for 1 h and iodomethane (5.06 mL, 81.3 mmol) was then added. After stirring for 30 min, the solution was allowed to reach room temperature. The mixture was extracted with ether and the organic extract was washed with saturated NH_4Cl solution, saturated $NaHCO_3$, and brine. The dried solution (Na_2SO_4) was concentrated in vacuo and the residue was purified using flash chromatography (5% then 10% ethyl acetate in hexanes) to give **6** as colorless crystals (2.47 g, 63% after crystallization from hexanes, −15°C). R_f 0.36 {ethyl acetate/hexane (2/8)}; mp 42°C; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89–0.94 (m, 12H), 1.21 (d, 3H, $J=6.5$ Hz), 1.25 (m, 1H), 1.59 (m, 1H), 1.68 (m, 1H), 2.37 (m, 1H), 3.88 (m, 1H), 4.21 (m, 1H), 4.28 (m, 1H), 4.46 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.7, 17.9, 18.2, 22.4, 22.8, 25.8, 28.4, 35.6, 42.00, 58.4, 63.2, 153.6, 177.5; IR ν_{max} (KBr, $CHCl_3$) 2960, 2933, 2874, 2359, 2341, 1781, 1699, 1488, 1459, 1386, 1300, 1249, 1225, 1203, 1120, 1092, 1058, 1023, 991, 968, 774, 688 cm^{-1}; HRMS *m/z* calcd for $C_{13}H_{23}NO_3$ (M+Na) 241.168, found 241.158; $[\alpha]=+83$ ($CHCl_3$, *c* 1.05).

4.5. (2*S*)-2,4-Dimethyl-1-pentanol 7

Lithium aluminum hydride (1.15 g, 30.3 mmol) was added to a solution of **6** (2.44 g, 10.1 mmol) in THF (20 mL) at 0°C. After 10 min, excess $LiAlH_4$ was neutralized by addition of saturated aqueous NH_4Cl solution. The mixture was extracted with ether. The organic extracts were dried (Na_2SO_4,) evaporated, and the residue purified by flash chromatography (10% ethyl acetate in hexanes) to provide **7** (1.02 g, 87%) as a colorless oil. R_f 0.23 {ethyl acetate/hexane (2/8)}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, 3H, $J=6.5$ Hz), 0.919 (d, 3H, $J=6.5$ Hz), 0.923 (d, 3H, $J=6.6$ Hz), 1.03 (m, 1H), 1.21 (m, 1H), 1.4 (m, 1H), 1.69 (m, 1H), 3.41 (m, 1H), 3.51 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.7, 22.1, 23.5, 25.2, 33.4, 42.7, 68.7; IR ν_{max} (KBr, $CHCl_3$) 3331, 2956, 2925, 2871, 1469, 1384, 1366, 1260, 1217, 1170, 1075, 1040, 991, 973, 939, 909, 870, 806 cm^{-1}; $[\alpha]=-18.3$ ($CHCl_3$, *c* 1.12).

4.6. (2*S*)-2,4-Dimethyl-1-pentanal 8

A solution of oxalyl chloride (0.312 mL, 3.6 mmol) in 20 mL of CH_2Cl_2 was cooled to −78°C and anhydrous dimethylsulfoxide (0.275 mL, 3.9 mmol) was added. After stirring for 30 min, a solution of **7** (350 mg, 2.9 mmol) in CH_2Cl_2 (4 mL) was added. The resulting white suspension was stirred at −78°C for 30 min and triethylamine (2.1 mL, 14.8 mmol) was then added. After stirring for 1 h, the solution was warmed to room temperature. The mixture was washed with 1N aqueous HCl solution, saturated $NaHCO_3$, and brine. The dried solution (Na_2SO_4) was concentrated in vacuo to provide **8** as an orange oil (300 mg, 91%), which was used immediately. R_f 0.54 {ethyl cetate/hexane (2/8)}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, 3H, $J=6.5$ Hz), 0.94 (d, 3H, $J=6.5$ Hz), 1.09 (d, 3H, $J=7$ Hz), 1.21 (m, 1H), 1.62 (m, 1H), 1.68 (m, 1H), 2.42 (m, 1H), 9.61 (d, 1H, $J=2.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.68, 22.19, 22.87, 25.55, 39.71, 44.44, 205.34.

4.7. (4*S*)-4-Isopropyl-3-[(2′*R*,3′*R*,4′*S*)-2′,4′,6′-trimethyl-3′-hydroxyheptyl)]-2-oxazolidinone 9

To a solution of **4** (315 mg, 1.7 mmol) in CH_2Cl_2 (5 mL) at 0°C was added triethylamine (0.275 mL, 1.9 mmol). A solution of dibutylboron triflate (1 M, 2.05 mL, 2.05 mmol) in CH_2Cl_2 was then added, and the mixture was stirred for 1 h at 0°C. In a separate flask, a solution of Et_2AlCl (1 M, 5.1 mL, 5.1 mmol) in hexanes was diluted with CH_2Cl_2 (5 mL) and cooled to −78°C. Aldehyde **8** (300 mg, 2.6 mmol) in CH_2Cl_2 (2 mL) was then added at −78°C. After stirring for 5 min, the boron enolate solution was added via cannula. The mixture was stirred for 5 h and then allowed to reach room temperature over 12 h. The reaction mixture was then cooled to −78°C, and a mixture of methanol (6 mL) and of 30% aqueous H_2O_2 (2 mL) was added. The mixture was allowed to warm to 0°C. The mixture was extracted with ether and the organic extract was washed with saturated $NaHCO_3$, saturated NH_4Cl solution, and brine. The solution was dried (Na_2SO_4), concentrated in vacuo, and the residue was then purified using flash chromatography (10% ethyl acetate in hexanes) to provide **9** as colorless crystals (98 mg, 21% from two steps and crystallization from hexanes, −15°C). R_f 0.25 {ethyl acetate/hexane (2/8)}; mp 61–62°C; ^1H NMR (500 MHz, $CDCl_3$) δ 0.84–0.92 (m, 15H), 1.10 (d, 3H, $J=6.7$ Hz), 1.16 (m, 1H), 1.25 (m, 1H), 1.65 (m, 1H),

1.74 (m, 1H), 2.4 (m, 1H), 3.56 (m, 1H), 4.03 (m, 1H), 4.30 (m, 2H), 4.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.44, 14.57, 14.78, 17.99, 22.34, 23.07, 25.02, 28.56, 32.36, 40.58, 43.29, 59.12, 63.42, 78.00, 152.00, 177.13; IR ν_{max} (KBr, $CHCl_3$) 3530, 2959, 1779, 1670, 1464, 1385, 1301, 1204, 1142, 1109, 1056, 986, 775, 709 cm^{-1}; HRMS m/z calcd for $C_{16}H_{29}NO_4$ (M+Na) 322.1994, found 322.1978; $[\alpha]=+57.5$ ($CHCl_3$, c 1.02).

4.8. (4*S*)-4-Isopropyl-3-[(2′*R*,3′*R*,4′*S*)-2′,4′,6′-trimethyl-3′-*tert*-butyl-dimethylsilylo-xyheptyl)]-2-oxazolidinone 10

2,6-Lutidine (0.1 mL, 0.86 mmol) and *tert*-butyldimethyltrifluoromethane sulfonate (0.104 mL, 0.46 mmol) were added to a solution of **9** (90 mg, 0.3 mmol) in CH_2Cl_2 (1 mL). The solution was stirred for 1.5 h at room temperature and then poured into a mixture of ether and saturated aqueous $NaHCO_3$. The organic phase was separated and washed with saturated brine, dried (Na_2SO_4), and evaporated. The residue was then purified using flash chromatography (10% ethyl acetate in hexanes) to provide the silyl ether **10** as a white solid (89 mg, 65%). R_f 0.28 {ethyl acetate/hexane (1/9)}; mp 76–78°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.12 (s, 3H), 0.83–0.95 (m, 24H), 1.14–1.20 (m, 5H, including d, 3H, $J=6.7$ Hz), 1.62 (m, 1H), 1.67 (m, 1H), 2.4 (m, 1H), 4.04 (m, 1H), 4.11 (m, 1H), 4.24 (m, 2H), 4.44 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.57, −4.07, 13.50, 13.83, 14.46, 18.22, 18.44, 21.81, 23.6, 25.1, 26.17 (3 overlapping carbons), 28.43, 33.18, 44.06, 44.44, 58.87, 62.72, 75.07, 153.66, 175.23; IR ν_{max} (KBr, $CHCl_3$) 2956, 2929, 1782, 1698, 1464, 1386, 1372, 1300, 1250, 1226, 1204, 1120, 1088, 1058, 1015, 990, 838, 776 cm^{-1}; HRMS m/z calcd for $C_{22}H_{43}NO_4Si$ (M+Na) 436.2859, found 436.2856; $[\alpha]=-7.0$ ($CHCl_3$, c 1.02).

4.9. (2*R*,3*R*,4*S*)-2,4,6-Trimethyl-3-*tert*-butyldimethyl-silyloxyheptanoic acid 1

A solution of **10** (90 mg, 0.22 mmol) in THF–H_2O (3/1, 1 mL) was treated at 0°C with H_2O_2 (6 equiv., 0.15 mL of 30% aqueous H_2O_2) and LiOH (11 mg, 0.46 mmol). The resulting mixture was stirred at 0°C for 3 h, and then warmed to room temperature and stirred for 12 h. Excess peroxide was quenched at 0°C by the addition of 1.5N aqueous Na_2SO_3 (1 mL). The solution was poured into a mixture of ether and 1N aqueous HCl. The organic phase was separated and washed with saturated brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was then purified using flash chromatography (10% ethyl acetate in hexanes+1% acetic acid) to give **1** as a colorless oil (50 mg, 76%). R_f 0.57 {ethyl acetate/hexane (1/9)+1% AcOH}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.08 (s, 3H), 0.81–0.89 (m, 18H), 1.09 (m, 1H), 1.15–1.19 (m, 4H, including d, 3H, $J=7.1$ Hz), 1.6 (m, 1H), 1.7 (m, 1H), 2.64 (m, 1H), 3.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.44, −4.04, 14.34, 15.00, 18.34, 21.76, 23.65, 25.23, 26.04 (3 overlapping carbons), 34.15, 42.23, 44.08, 78.10, 180.47; IR ν_{max} (KBr, $CHCl_3$) 2960, 2933, 2873, 1781, 1699, 1487, 1465, 1386, 1299, 1284, 1249, 1225, 1203, 1092, 1058, 992, 774, 701 cm^{-1}; HRMS m/z calcd for $C_{16}H_{34}O_3Si$ (M+Na) 325.2175, found 325.2160; $[\alpha]=-13.55$ ($CHCl_3$, c 1.07).

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 175153 & 175154. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223–336033 or e-mail: deposit@ccdc.cam.ac.uk.

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