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Novel stereoselective syntheses of *N*-octyl-β-valienamine (NOV) and *N*-octyl-4-*epi*-β-valienamine (NOEV) from (−)-shikimic acid†‡

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N-Octyl-β-valienamine (NOV) **1** and *N*-octyl-4-*epi*-β-valienamine (NOEV) **2** are potent chemical chaperone drug candidates for the therapy of lysosomal storage disorders. Novel stereoselective syntheses of NOV **1** and NOEV **2** starting from naturally abundant (−)-shikimic acid are described in this article. The common key intermediate compound **5** was first synthesized from readily available (−)-shikimic acid *via* 9 steps in 50% yield. Compound **5** was then converted to NOV **1** *via* 5 steps in 61% yield, and it was also converted to NOEV **2** *via* 8 steps in 38% yield. In summary, NOV **1** was synthesized *via* 14 steps in 31% overall yield; and NOEV **2** was synthesized *via* 17 steps in 19% overall yield.

Introduction

Lysosomal storage diseases (LSDs) are a group of inborn errors of metabolism caused by a deficiency of one or more lysosomal enzymes such as hydrolases, proteases, lipases, sulfatases, *etc.*, that are involved in macromolecule degradation and recycling.[1] G_{M1}-gangliosidosis and Gaucher disease are two types of prevalent LSDs resulting from deficiencies of β-galactosidase and β-glucosidase, respectively.[2,3] The chaperone therapy strategy has been developed as an effective approach for the treatment of various LSDs,[4] including G_{M1}-gangliosidosis and Gaucher disease.[5,6] Recently, it was found that *N*-octyl-β-valienamine (NOV) **1** (Fig. 1) could be used as a potent chemical chaperone for the treatment of Gaucher disease by stabilizing β-glucosidase,[7] and *N*-octyl-4-*epi*-β-valienamine (NOEV) **2** (see Fig. 1) could be used as a potent chemical chaperone for treatment of G_{M1}-gangliosidosis by stabilizing β-galactosidase.[8]

Since NOV **1** and NOEV **2** are good candidates for potent chemical chaperone therapy for LSDs, chemists have been interested in developing efficient and practical syntheses of these two important compounds. NOV **1** was first synthesized from β-valienamine by Ogawa *et al.* in 1996.[9] NOV **1** was also synthesized from (−)-*vibo*-quercitol by Kuno *et al.* in 2011.[10] NOEV **2** was first synthesized from NOV **1** by Ogawa *et al.* in 2002[11] *via* chiral alcohol epimerization at the C-4 position through an oxidation–reduction sequence. NOEV **2** was also synthesized from (+)-*proto*-quercitol by Kuno *et al.* in 2011.[10] An improved concise synthesis of NOEV **2** from (+)-*proto*-quercitol has been reported by Kuno's group in 2013.[12] Both NOV **1** and NOEV **2** could be synthesized from the Diels–Alder *endo*-adduct of furan and acrylic acid. The above racemic *endo*-adduct was first resolved into the enantiomerically pure (+)-*endo*-adduct and (−)-*endo*-adduct by use of (*R*)-(+)- and (*S*)-(−)-α-methylbenzylamine.[13] NOV **1** and NOEV **2** were then synthesized from the (−)-*endo*-adduct and (+)-*endo*-adduct,[14] respectively.

(−)-Shikimic acid (see Fig. 1) can be obtained from many natural plants,[15] microbial engineering processes[16] and chemical syntheses.[17] It is noted that (−)-shikimic acid is particularly abundant in Chinese star anise (*Illicium verum*),[15e,18] and thus can be readily manufactured in a large quantity by extraction from the Chinese star anise.[18b] (−)-Shikimic acid has captured worldwide attention[19] in recent decades due to its wide use in the syntheses of drugs, natural products and many useful chiral intermediates. Recently, we have been engaged in developing novel stereoselective syntheses of various pharmaceutically valuable molecules from (−)-shikimic acid.[20] To continue our research programs, we have just studied highly stereoselective, efficient and practical syntheses of NOV **1** and NOEV **2** by using

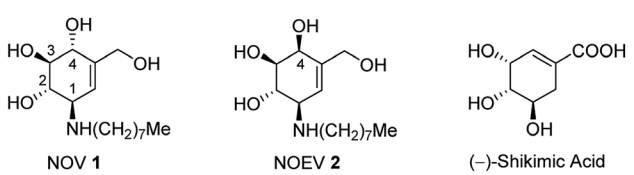

Fig. 1 The structures of some related compounds.

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† Dedicated to Professor Li-Xin Dai in SIOC on the occasion of his 95th birthday.

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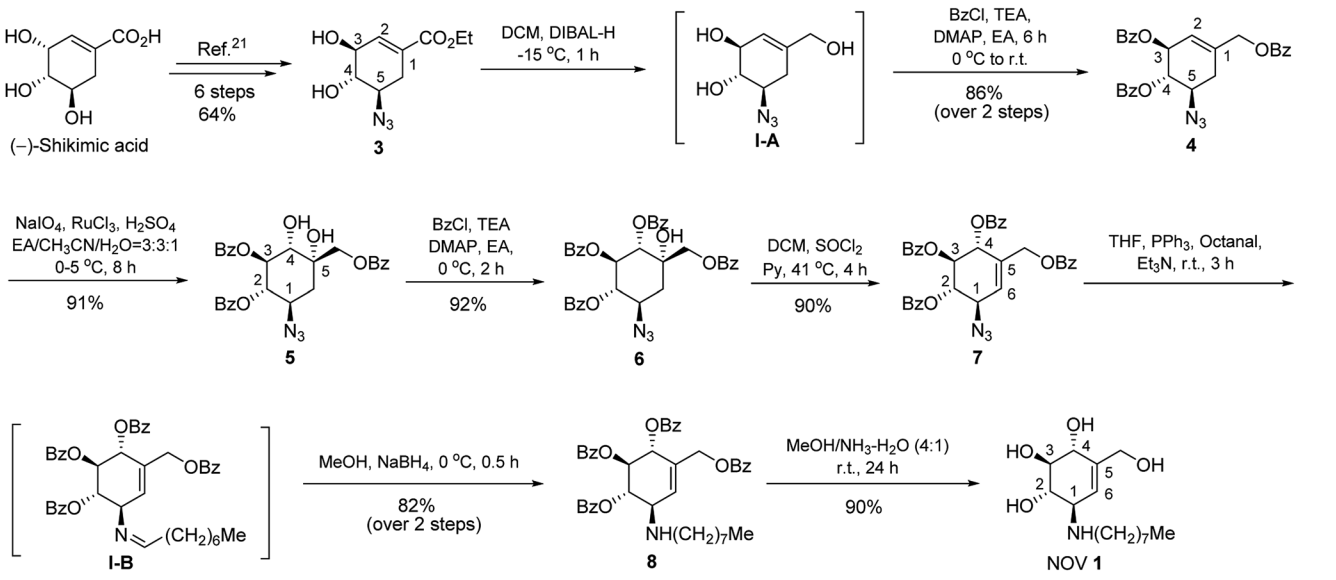
(−)-shikimic acid as the starting material, and herein we want to report the details of these syntheses.

Results and discussion

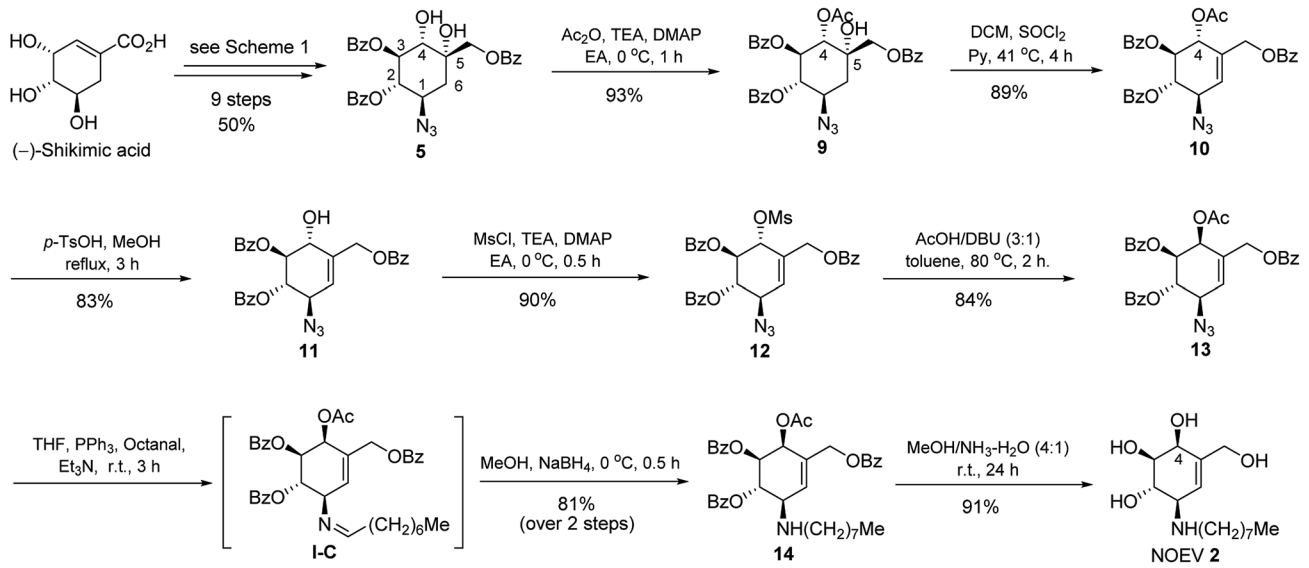
The new stereoselective total synthesis of NOV **1** starting from (−)-shikimic acid is depicted in Scheme 1. As can be seen from Scheme 1, our synthetic efforts began with compound **3**, which could be easily prepared from the commercially available (−)-shikimic acid *via* 6 steps in 64% overall yield according to a previous report.[21] Compound **3** was first treated with 3.0 equivalents of diisobutylaluminum hydride (DIBAL-H) at −15 °C in dichloromethane (DCM), the ester group (CO_2Et) was reduced to produce an intermediate compound **I-A** (as shown in the parenthesis in Scheme 1), which was used as such in the next step without purification. When compound **I-A** was exposed to 5.0 equivalents of benzoyl chloride (BzCl), 8.0 equivalents of triethylamine (TEA) and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) at 0 °C to room temperature in ethyl acetate, compound **4** was thus obtained in 86% yield (over 2 steps). Compound **4** was then treated with 1.5 equivalents of sodium periodate ($NaIO_4$), 1.0 equivalent of sulfuric acid and 0.002 equivalent of ruthenium trichloride ($RuCl_3$) at 0 to 5 °C for 8 h in a mixed solvent of ethyl acetate, acetonitrile and water ($EtOAc/CH_3CN/H_2O$, 3 : 3 : 1), Ru-catalyzed highly stereoselective dihydroxylation[22] took place smoothly to afford compound **5** in 91% yield. It was observed that the addition of sulfuric acid could significantly reduce the loading of the ruthenium catalyst, which was consistent with Plietker's report.[23] The stereochemistry of this dihydroxylation is worthy of note, the ruthenium catalyst coordinated with the double bond in the opposite direction of the OBz group at the C-3 position of compound **4** due to its high steric hindrance, so that two hydroxyls at C-4 and C-5 positions of compound **5** should have the desired downward orientation.

Subsequently, compound **5** was treated with 1.5 equivalents of benzoyl chloride (BzCl), 2.0 equivalents of triethylamine and a catalytic amount of DMAP at 0 °C in ethyl acetate, selective benzylation of the secondary hydroxyl group at the C-4 position occurred smoothly to give compound **6** in 92% yield. Compound **6** was then exposed to 5.0 equivalents of thionyl chloride ($SOCl_2$) and 3.0 equivalents of pyridine under reflux (41 °C) for 4 h in dichloromethane, elimination occurred to afford compound **7** in 90% yield. Next, Staudinger reduction[24] of compound **7** with 1.5 equivalents of triphenylphosphine at room temperature in anhydrous tetrahydrofuran provided an aza–ylide intermediate. The aza–ylide was exposed to 3.0 equivalents of octanal and 1.0 equivalent of triethylamine to form an unstable imine **I-B** (as shown in the parenthesis in Scheme 1), which was used as such in the next step without purification. The unstable imine **I-B** was immediately reduced by 4.0 equivalents of sodium borohydride ($NaBH_4$) at 0 °C for 0.5 h in methanol to afford compound **8** in 82% yield (over 2 steps). Finally, when a solution of compound **8** in a mixed solvent of methanol and concentrated aqueous ammonia ($CH_3OH/NH_3\cdot H_2O$, 4 : 1) was stirred at room temperature for approximately 24 h, all of the four benzoyl (Bz) groups in compound **8** could be removed in one-pot to furnish the desired NOV **1** in 90% yield.

The new stereoselective total synthesis of NOEV **2** starting from (−)-shikimic acid is depicted in Scheme 2. As can be seen from Scheme 2, (−)-shikimic acid was first converted to compound **5** in 50% yield by the same 9 steps as per the Scheme 1. Compound **5** was then treated with 2.0 equivalents of acetic anhydride (Ac_2O), 3.0 equivalents of triethylamine and a catalytic amount of DMAP at 0 °C in ethyl acetate, the less hindered secondary hydroxyl at the C-4 position was selectively acetylated to afford compound **9** in 93% yield. Next, when compound **9** was exposed to 5.0 equivalents of thionyl chloride ($SOCl_2$) and 3.0 equivalents of pyridine (Py) under reflux (41 °C) in CH_2Cl_2, regioselective elimination occurred smoothly to furnish an



Scheme 1 The stereoselective synthesis of *N*-octyl-β-valienamine (NOV) **1** starting from (−)-shikimic acid.



Scheme 2 The stereoselective synthesis of *N*-octyl-4-*epi*-β-valienamine (NOEV) **2** starting from (–)-shikimic acid.

olefinic compound **10** in 89% yield. We then attempted to selectively hydrolyze the acetoxy (AcO) group at the C-4 position of compound **10** in the presence of three benzoxy (BzO) groups. We eventually found the right key after a lot of trial and error. It was found that when compound **10** was treated with 2.0 equivalents of *p*-toluenesulfonic acid (*p*-TsOH) under reflux in methanol for 3 h, the desired compound **11** was obtained in 83% yield. Compound **11** was exposed to 2.0 equivalents of trimethylamine, 1.5 equivalents of methanesulfonyl chloride (MsCl), and a catalytic amount of DMAP at 0 °C in ethyl acetate, methanesulfonate **12** was thus obtained in 90% yield. According to a known method,[25] compound **12** was then treated with a mixture of acetic acid and 1,8-diazabicyclo[5.4.0]undec-7-ene (AcOH/DBU, 3 : 1) in toluene at 80 °C for 2 h, compound **13** was thus obtained in 84% yield.

Subsequently, Staudinger reduction[24] of compound **13** with 1.5 equivalents of triphenylphosphine at room temperature in anhydrous tetrahydrofuran provided an aza–ylide intermediate. The aza–ylide was then exposed to 3.0 equivalents of octanal and 1.0 equivalent of triethylamine to form an unstable imine **I-C** (as shown in the parenthesis in Scheme 2), which was used as such in the next step without purification. The unstable imine **I-C** was immediately reduced by 4.0 equivalents of sodium borohydride ($NaBH_4$) at 0 °C for 0.5 h in methanol to afford compound **14** in 81% yield (over 2 steps). Finally, when a solution of compound **14** in a mixed solvent of methanol and concentrated aqueous ammonia ($CH_3OH/NH_3 \cdot H_2O$, 4 : 1) was stirred at room temperature for approximately 24 h, all the four protecting groups (Bz and Ac) in compound **14** could be removed in one-pot to furnish the desired NOEV **2** in 91% yield.

Conclusions

In conclusion, we have successfully developed novel total syntheses of NOV **1** and NOEV **2** using naturally abundant and commercially available (–)-shikimic acid as the starting material. The target compound NOV **1** was synthesized *via* 14 steps in 31% overall yield, and the other target compound NOEV **2** was synthesized *via* 17 steps in 19% overall yield. The present synthetic approaches might also be appropriate for the syntheses of congeners and derivatives of NOV **1** and NOEV **2**, which are potent chemical chaperone drug candidates for the therapy of LSDs. In comparison to previous reports,[9–14] the presented syntheses of NOV **1** and NOEV **2** have some advantages, such as the mildness of the reaction conditions, the use of inexpensive reagents in all steps, the good to high yields, and the ease of experimental operations.

Experimental

General

^1H and ^{13}C NMR spectra were acquired on a Bruker AM-400 instrument. Chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on a Nicolet Magna IR-550 spectrometer. MS spectra were recorded on a Mariner Mass Spectrum (ESI) equipment. Optical rotations of chiral compounds were measured on a PerkinElmer polarimeter at room temperature. Melting points were determined on a Mel-TEMP II melting point apparatus. Column chromatography was performed on silica gel. All chemicals are analytically pure. Compound **3** was prepared according to the previously reported procedures.[21]

(3*S*,4*S*,5*R*)-5-Azido-1-benzoyloxymethyl-3,4-dibenzoyloxycyclohex-1-ene 4. To a solution of compound **3** (10.00 g, 44.01 mmol) in dichloromethane (300 mL) was slowly added DIBAL-H (1.0 M in hexane, 135 mL, 135.0 mmol) over 15 min at −15 °C. When the addition was finished, the mixture was further stirred at −15 °C for 1 h. MeOH (20 mL) was added to quench the reaction, and the mixture was vigorously stirred at −15 °C for 0.5 h. The solvents were then removed under vacuum to give a white solid residue. Anhydrous methanol (40 mL) was added, the turbid mixture was vigorously stirred at room temperature

for 2 h and filtered by suction, the filter cake was washed with anhydrous methanol (2 × 20 mL), and the filtrate was concentrated under vacuum to give a pale-yellow oily residue. Toluene (100 mL) was added, and the mixture was vigorously stirred for 15 min. After toluene was removed by vacuum distillation, anhydrous EtOAc (300 mL) was added, and the resulting solution was cooled to 0 °C by an ice bath. Et_3N (35.62 g, 352.0 mmol), BzCl (30.94 g, 220.1 mmol), and a catalytic amount of DMAP (538.0 mg, 4.404 mmol) were then added in turn. After the addition, the reaction mixture was then removed from the cold bath and allowed to warm to room temperature while being stirred for 6 h. The reaction was quenched by adding a dilute aqueous solution of hydrochloric acid (2 M, 200 mL). After the mixture was vigorously stirred for 5 min, the two phases were separated, and the aqueous phase was extracted again with ethyl acetate (200 mL). The organic extracts were combined and washed successively with a dilute aqueous solution of K_2CO_3 (10% w/w, 100 mL) and brine (20 mL). The organic solution was then dried over anhydrous $MgSO_4$. Evaporation of solvent under vacuum gave a crude product which was purified by flash chromatography (eluent: ethyl acetate/hexane = 1 : 20) to afford compound **4** (18.83 g, 37.85 mmol) as a colorless oil in 86% yield. $[\alpha]_D^{20}$ = +103 (*c* 0.9, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–7.93 (m, 6H, Ar-H in Bz), 7.60–7.48 (m, 3H, Ar-H in Bz), 7.48–7.35 (m, 6H, Ar-H in Bz), 5.95–5.90 (m, 2H, H-2 and H-3), 5.71 (dd, J_1 = 10.5, J_2 = 7.6 Hz, 1H, H-4), 4.83 (d, J = 13.6 Hz, 1H, C*H*HOBz), 4.81 (d, J = 13.6 Hz, 1H, CH*H*OBz), 4.11–4.04 (m, 1H, H-5), 2.73 (dd, J_1 = 17.6 Hz, J_2 = 5.8 Hz, 1H, H-6), 2.47 (dd, J_1 = 17.5 Hz, J_2 = 10.1 Hz, 1H, the other H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.07, 166.05, 165.68, 134.29, 133.45, 133.38, 133.36, 129.89, 129.86, 129.85, 129.74 (2C), 129.57, 129.38, 129.17, 128.56, 128.48 (2C), 128.47 (2C), 122.90, 73.81, 72.36, 66.27, 58.60, 31.47. HRMS (ESI) calcd for $C_{28}H_{23}N_3O_6Na$ $[M + Na]^+$: 520.1485; found: 520.1479. IR (neat) ν = 2926, 2102 (N_3), 1726 (C═O), 1451, 1265, 1176, 1108, 1069, 1027, 710 cm^{-1}.

(1*R*,2*S*,3*S*,4*S*,5*S*)-1-Azido-5-benzoyloxymethyl-2,3-dibenzoyloxy-4,5-dihydroxycyclohexane 5. The powdered $NaIO_4$ (3.870 g, 18.09 mmol) was added into an aqueous solution of H_2SO_4 (12.0 mL, 1.0 M, 12.0 mmol). The mixture was stirred at room temperature for 10 min, and then an aqueous solution of $RuCl_3$ (0.25 mL, 0.1 M, 0.025 mmol) was added. The resulting solution was stirred at room temperature until the color turned bright yellow, and then the temperature was cooled down to 0 °C by an ice-bath. A solution of compound **4** (6.000 g, 12.06 mmol) in a mixed solvent of ethyl acetate (36 mL) and CH_3CN (36 mL) was added at 0 °C. The mixture was then vigorously stirred at 0 °C to 5 °C for approximately 8 h. After the reaction was complete (checked by TLC, eluent: ethyl acetate/hexane = 1 : 3), ethyl acetate (100 mL), a saturated aqueous solution of $Na_2S_2O_3$ (60 mL) and a saturated aqueous solution of $NaHCO_3$ (30 mL) were added, and the mixture was vigorously stirred for 15 min. The phases were separated, and the aqueous phase was extracted twice with ethyl acetate (2 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, and then filtered. Concentration of the filtrate under vacuum gave a crude product which was purified by flash chromatography (eluent: ethyl acetate/hexane = 1 : 4) to afford compound **5** (5.835 g, 10.98 mmol) as white crystals in 91% yield. Mp 187–190 °C. $[\alpha]_D^{20}$ = +61 (*c* 0.7, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.3 Hz, 2H, Ar-H in Bz), 7.96 (d, J = 7.4 Hz, 2H, Ar-H in Bz), 7.91 (d, J = 7.4 Hz, 2H, Ar-H in Bz), 7.60 (t, J = 7.4 Hz, 1H, Ar-H in Bz), 7.52–7.40 (m, 4H, Ar-H in Bz), 7.35–7.28 (m, 4H, Ar-H in Bz), 5.65 (dd, J_1 = 9.7 Hz, J_2 = 9.6 Hz, 1H, H-3), 5.46 (dd, J_1 = 10.1 Hz, J_2 = 10.0 Hz, 1H, H-2), 4.54 (d, J = 11.3 Hz, 1H, C*H*HOBz), 4.27 (d, J = 11.3 Hz, 1H, CH*H*OBz), 4.26–4.20 (m, 1H, H-1), 3.86 (d, J = 9.5 Hz, 1H, H-4), 2.38 (dd, J_1 = 14.0 Hz, J_2 = 4.7 Hz, 1H, H-6), 1.83 (dd, J_1 = 14.0 Hz, J_2 = 12.6 Hz, 1H, the other H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.33, 166.89, 165.85, 133.78, 133.52, 133.42, 129.90 (2C), 129.88, 129.81 (2C), 129.06, 129.05, 128.94 (2C), 128.87 (2C), 128.68 (2C), 128.42 (2C), 74.62, 74.08, 72.73, 72.27, 67.19, 57.87, 34.88. HRMS (ESI) calcd for $C_{28}H_{25}N_3O_8Na$ $[M + Na]^+$: 554.1539; found: 554.1544. IR (KBr film) ν = 3446 (O–H), 2094 (N_3), 1731 (C═O), 1451, 1275, 1116, 1068, 1025, 708 cm^{-1}.

(1*R*,2*S*,3*R*,4*S*,5*S*)-1-Azido-5-benzoyloxymethyl-2,3,4-tribenzoyloxy-5-hydroxycyclohexane 6. To a solution of compound **5** (3.000 g, 5.644 mmol) in ethyl acetate (50 mL) was added triethylamine (1.143 g, 11.29 mmol). The resulting solution was cooled down to 0 °C by an ice bath, and then benzoyl chloride (1.195 g, 8.501 mmol) was added. After the addition was finished, the mixture was further stirred at 0 °C for 2 h. The reaction was quenched by adding a dilute aqueous solution of HCl (1 M, 20 mL), after which the two phases were separated, and the aqueous phase was extracted twice with ethyl acetate (2 × 25 mL). The combined organic extracts were then washed with a dilute aqueous solution of potassium carbonate (1 M, 20 mL). The organic extracts were dried over anhydrous $MgSO_4$. Evaporation of solvent under vacuum gave a light yellow liquid which was purified by flash chromatography (eluent: ethyl acetate/hexane = 1 : 8) to afford compound **6** (3.300 g, 5.192 mmol) as white crystals in 92% yield. Mp 81–82 °C. $[\alpha]_D^{20}$ = +29 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.3 Hz, 2H, Ar-H in Bz), 7.90 (d, J = 7.3 Hz, 2H, Ar-H in Bz), 7.79 (d, J = 7.3 Hz, 2H, Ar-H in Bz), 7.65 (d, J = 7.4 Hz, 2H, Ar-H in Bz), 7.50–7.23 (m, 8H, Ar-H in Bz), 7.21–7.08 (m, 4H, Ar-H in Bz), 6.06 (dd, J_1 = 10.0 Hz, J_2 = 10.01 Hz, 1H, H-3), 5.63 (d, J = 10.0 Hz, 1H, H-4), 5.54 (dd, J_1 = 10.1 Hz, J_2 = 9.9 Hz, 1H, H-2), 4.38 (d, J = 11.6 Hz, 1H, C*H*HOBz), 4.27–4.20 (m, 1H, H-1), 4.18 (d, J = 11.6 Hz, 1H, CH*H*OBz), 2.38 (dd, J_1 = 14.2 Hz, J_2 = 4.7 Hz, 1H, H-6), 1.91 (dd, J_1 = 14.2 Hz, J_2 = 11.0 Hz, 1H, the other H-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.37, 165.93, 165.67, 165.34, 133.56, 133.50, 133.42, 133.20, 129.88 (2C), 129.84 (2C), 129.76 (2C), 129.64 (2C), 128.99, 128.89, 128.70, 128.52, 128.49 (2C), 128.44 (2C), 128.41 (2C), 128.24 (2C), 74.40, 73.59, 72.69, 71.38, 67.52, 57.85, 35.69. HRMS (ESI) calcd for $C_{35}H_{29}N_3O_9Na$ $[M + Na]^+$: 658.1801; found: 658.1806. IR (KBr film) ν = 3503 (O–H), 2107 (N_3), 1734 (C═O), 1451, 1319, 1266, 1096, 1068, 1027, 708 cm^{-1}.

(1*R*,2*S*,3*S*,4*R*)-1-Azido-5-benzoyloxymethyl-2,3,4-tribenzoyloxy-cyclohex-5-ene 7. Compound **6** (2.000 g, 3.146 mmol) was dissolved in CH_2Cl_2 (25 mL), then the resulting solution was cooled down to 0 °C by an ice bath. $SOCl_2$ (1.872 g, 15.74 mmol) and pyridine (747.5 mg, 9.450 mmol) were added in turn. After the addition was finished, the ice bath was removed and the mixture was heated and stirred under reflux for approximately

4 h. After the reaction was complete (checked by TLC, eluent: ethyl acetate/hexane = 1 : 5), the mixture was cooled down to room temperature. A dilute aqueous solution of hydrochloric acid (1 M, 20 mL) was added. After the mixture was further stirred for 5 min, the two phases were separated, and the aqueous solution was extracted twice with dichloromethane (2 × 25 mL). The organic extracts were combined, and successively washed with a dilute aqueous solution of potassium carbonate (2 M, 20 mL) and brine (10 mL). The organic extracts were dried over anhydrous $MgSO_4$, and then concentrated under vacuum to give the crude product, which was purified by flash chromatography (eluent: ethyl acetate/hexane = 1 : 6) to afford compound **7** (1.750 g, 2.833 mmol) as white crystals in 90% yield. Mp 56–57 °C. $[\alpha]_D^{20} = -65$ (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, $J = 7.5$ Hz, 2H, Ar-H in Bz), 7.93 (d, $J = 7.5$ Hz, 2H, Ar-H in Bz), 7.92 (d, $J = 7.5$ Hz, 2H, Ar-H in Bz), 7.81 (d, $J = 7.5$ Hz, 2H, Ar-H in Bz), 7.57–7.46 (m, 3H, Ar-H in Bz), 7.42–7.38 (m, 3H, Ar-H in Bz), 7.36–7.30 (m, 4H, Ar-H in Bz), 7.30–7.24 (m, 2H, Ar-H in Bz), 6.40 (d, $J = 7.6$ Hz, 1H, H-4), 6.07 (d, $J = 1.9$ Hz, 1H, H-6, olefinic proton), 5.97 (dd, $J_1 = 10.5$ Hz, $J_2 = 7.6$ Hz, 1H, H-3), 5.81 (dd, $J_1 = 10.5$ Hz, $J_2 = 8.2$ Hz, 1H, H-2), 4.94 (d, $J = 12.0$ Hz, 1H, ab peak, C*H*HOBz), 4.92 (d, $J = 12.0$ Hz, 1H, ab peak, CH*H*OBz), 4.57 (dd, $J_1 = 8.2$ Hz, $J_2 = 1.9$ Hz, 1H, H-1). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.82, 165.73, 165.63, 165.53, 134.81, 133.50, 133.32 (2C), 133.30, 129.86 (2C), 129.83 (2C), 129.75 (2C), 129.39 (2C), 128.87 (2C), 128.75 (2C), 128.68, 128.48 (2C), 128.45, 128.41, 128.31, 125.76, 72.08, 71.99, 71.02, 63.35, 60.83. HRMS (ESI) calcd for $C_{35}H_{27}N_3O_8Na$ $[M + Na]^+$: 640.1696; found: 640.1697. IR (KBr film) $\nu = 2104$ (N_3), 1730 (C=O), 1451, 1315, 1264, 1094, 1068, 1025, 708 cm^{-1}.

(1*R*,2*S*,3*S*,4*R*)-5-Benzoyloxymethyl-1-octylamino-2,3,4-tribenzoyloxy-cyclohex-5-ene 8. To a solution of compound **7** (1.000 g, 1.619 mmol) in anhydrous tetrahydrofuran (10 mL) was added triphenylphosphine (636.8 mg, 2.428 mmol), triethylamine (164.0 mg, 1.621 mmol) and octanal (622.7 mg, 4.857 mmol) in turn. The resulting solution was stirred at room temperature for 3 h. After the reaction was complete (checked by TLC, eluent: ethyl acetate/hexane = 1 : 5), the solvent was evaporated under vacuum to give an oily residue which was dissolved in methanol (8 mL). The resulting solution was cooled to 0 °C. Sodium borohydride (245.0 mg, 6.476 mmol) was then slowly added into the mixture at 0 °C. After the addition was finished, the reaction mixture was further stirred at 0 °C for 30 min. After methanol was removed by vacuum distillation, water (20 mL) and ethyl acetate (30 mL) were added, and the mixture was vigorously stirred for 5 min. The phases were separated, and the aqueous phase was extracted again with ethyl acetate (25 mL). The organic extracts were combined and dried over anhydrous $MgSO_4$. Evaporation of solvent under vacuum gave a light yellow liquid which was purified by flash chromatography (eluent: ethyl acetate/hexane = 1 : 3) to afford compound **8** (934.7 mg, 1.328 mmol) as a colorless oil in 82% yield. $[\alpha]_D^{20} = -36$ (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, $J = 7.2$ Hz, 2H, Ar-H in Bz), 7.95–7.89 (m, 4H, Ar-H in Bz), 7.81 (d, $J = 7.2$ Hz, 2H, Ar-H in Bz), 7.56–7.48 (m, 3H, Ar-H in Bz), 7.42–7.35 (m, 3H, Ar-H in Bz), 7.36–7.28 (m, 4H, Ar-H in Bz), 7.28–7.21 (m, 2H, Ar-H in Bz), 6.39 (d, $J = 7.4$ Hz, 1H, H-4), 6.16 (d, $J = 1.9$ Hz, 1H, H-6, olefinic proton), 5.96 (dd, $J_1 = 10.3$ Hz, $J_2 = 7.4$ Hz, 1H, H-3), 5.73 (dd, $J_1 = 10.3$ Hz, $J_2 = 8.0$ Hz, 1H, H-2), 4.91 (d, $J = 11.8$ Hz, 1H, ab peak, C*H*HOBz), 4.89 (d, $J = 11.8$ Hz, 1H, ab peak, CH*H*OBz), 3.91 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.9$ Hz, 1H, H-1), 2.84–2.77 (m, 1H, NC*H*H), 2.62–2.56 (m, 1H, NCH*H*), 1.47–1.41 (m, 2H, CH_2), 1.23 (m, 10H, $(CH_2)_5$), 0.86 (t, $J = 6.9$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.16, 166.02, 165.84, 165.78, 133.28 (2C), 133.24 (2C), 133.10, 131.62 (2C), 131.24, 129.81 (2C), 129.77 (2C), 129.72 (2C), 129.65 (2C), 129.17, 129.03, 128.38 (2C), 128.35 (2C), 128.32 (2C), 128.23 (2C), 73.03, 71.74, 71.34, 64.14, 57.99, 45.63, 31.79, 30.28, 29.39, 29.22, 27.12, 22.64, 14.10. HRMS (ESI) calcd for $C_{43}H_{45}NO_8Na$ $[M + Na]^+$: 726.3043; found: 726.3045. IR (neat) $\nu =$ 3380 (N–H), 2926, 1728 (C=O), 1601, 1523, 1451, 1314, 1266, 1106, 1069, 1026, 709 cm^{-1}.

(1*R*,2*S*,3*S*,4*R*)-5-Hydroxymethyl-1-octylamino-2,3,4-trihydroxy-cyclohex-5-ene [*N*-octyl-β-valienamine] 1. Compound **8** (620.0 mg, 0.8809 mmol) was dissolved in a mixed solvent of methanol (8 mL) and ammonia hydrate (25% w/w, 2 mL), and the mixture was stirred at room temperature for approximately 24 h. The solution was then concentrated under vacuum to give an oily residue, which was dissolved in pure water (15 mL). The aqueous solution was twice washed with toluene (2 × 10 mL). The aqueous solution was concentrated to dryness under vacuum to give an oily residue, which was purified by chromatography on a column of Duolite-C20 resin (eluent: methanol/water/concentrated ammonia = 7 : 3 : 0.2) to furnish pure compound **1** (228.0 mg, 0.7933 mmol) as a colorless oil in 90% yield. $[\alpha]_D^{20} = -69$ (*c* 1.0, MeOH) {lit.[10] $[\alpha]_D^{25} = -69$ (*c* 1.0, MeOH)}. ^{1}H NMR (400 MHz, CD_3OD) δ 5.65 (d, $J = 2.0$ Hz, 1H, H-6), 4.26–3.99 (m, 3H, H-2, H-3 and H-4), 3.54–3.47 (m, 1H, C*H*HOH), 3.46–3.38 (m, 1H, CH*H*OH), 3.22 (dd, $J_1 = 5.9$ Hz, $J_2 =$ 2.0 Hz, 1H, H-1), 2.78–2.71 (m, 1H, NC*H*H), 2.60–2.52 (m, 1H, NCH*H*), 1.54–1.49 (m, 2H), 1.33–1.22 (m, 10H), 0.90 (t, $J =$ 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CD_3OD) δ 141.15, 122.84, 78.23, 73.91, 73.86, 62.93, 61.28, 47.20, 33.00, 30.81, 30.62, 30.39, 28.42, 23.73, 14.49. HRMS (ESI) calcd for $C_{15}H_{29}NO_4Na$ $[M + Na]^+$: 310.1994; found: 310.1998. IR (neat) $\nu =$ 3330–3400 (O–H, N–H), 2924, 1480, 1450, 1095, 908, 711 cm^{-1}.

(1*R*,2*S*,3*R*,4*S*,5*S*)-4-Acetoxy-1-azido-5-benzoyloxymethyl-2,3-dibenzoyloxy-5-hydroxyl-cyclohexane 9. To a solution of compound **5** (5.000 g, 9.407 mmol) in ethyl acetate (80 mL) was added triethylamine (2.856 g, 28.22 mmol) and DMAP (115.0 mg, 0.9413 mmol). The resulting solution was cooled down to 0 °C by an ice bath, and then acetic anhydride (1.920 g, 18.81 mmol) was added. After the addition was finished, the mixture was further stirred at 0 °C for 1 h. The reaction was quenched by adding a dilute aqueous solution of hydrochloric acid (1 M, 30 mL), after which two phases were separated, and the aqueous phase was extracted twice with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with a dilute aqueous solution of potassium carbonate (1 M, 20 mL), and then dried over anhydrous $MgSO_4$. Evaporation of solvent under vacuum gave a solid residue, which was purified by flash chromatography (eluent: ethyl acetate/hexane = 1 : 6) to give pure compound **9** (5.018 g, 8.749 mmol) as white crystals in 93% yield. Mp 169–171 °C. $[\alpha]_D^{20} = +74$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, $J = 7.4$ Hz, 2H, Ar-H in Bz), 7.97 (d, $J =$ 7.4 Hz, 2H, Ar-H in Bz), 7.88 (d, $J = 7.4$ Hz, 2H, Ar-H in Bz), 7.61

(t, J = 7.4 Hz, 1H, Ar-H in Bz), 7.52–7.45 (m, 4H, Ar-H in Bz), 7.38–7.31 (m, 4H, Ar-H in Bz), 5.95 (dd, J_1 = 10.0 Hz, J_2 = 10.01 Hz, 1H, H-3), 5.56 (dd, J_1 = 10.0 Hz, J_2 = 9.9 Hz, 1H, H-2), 5.51 (d, J = 10.1 Hz, 1H, H-4), 4.38 (d, J = 11.4 Hz, 1H, C*H*HOBz), 4.31–4.24 (m, 1H, H-1), 4.25 (d, J = 11.4 Hz, 1H, CH*H*OBz), 2.43 (dd, J_1 = 14.1 Hz, J_2 = 4.6 Hz, 1H, H-6), 1.98 (dd, J_1 = 14.1 Hz, J_2 = 11.2 Hz, 1H, the other H-6), 1.88 (s, 3H, CH_3 in Ac). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.33, 166.28, 165.83, 165.65, 133.67 (2C), 133.45 (2C), 133.41 (2C), 129.87 (2C), 129.83, 129.74, 129.12, 128.89, 128.68 (2C), 128.48 (2C), 128.41 (2C), 74.33, 72.59, 72.51, 71.52, 66.80, 57.80, 35.62, 20.43. HRMS (ESI) calcd for $C_{30}H_{27}N_3O_9Na$ [M + Na]$^+$: 596.1645; found: 596.1650. IR (KBr film) ν = 3462 (O–H), 2104 (N_3), 1729 (C=O), 1451, 1270, 1108, 1070, 1027, 709 cm^{-1}.

(1*R*,2*S*,3*S*,4*R*)-4-Acetoxy-1-azido-5-benzoyloxymethyl-2,3-di benzoyloxy-cyclohex-5-ene 10. Compound **9** (3.000 g, 5.231 mmol) was dissolved in CH_2Cl_2 (30 mL), then the resulting solution was cooled down to 0 °C by an ice bath. $SOCl_2$ (3.112 g, 26.16 mmol) and pyridine (1.242 g, 15.70 mmol) were added in turn. After the addition was finished, the ice bath was removed and the mixture was heated and stirred at reflux for approximately 4 h. After the reaction was complete (checked by TLC, eluent: ethyl acetate/hexane = 1 : 5), the mixture was cooled down to room temperature. A dilute aqueous solution of hydrochloric acid (1 M, 20 mL) was added. After the mixture was further stirred for 5 min, the two phases were separated, and the aqueous solution was extracted twice with dichloromethane (2 × 25 mL). The organic extracts were combined, and washed successively with a dilute aqueous solution of potassium carbonate (1 M, 20 mL) and brine (10 mL). The organic extracts were dried over anhydrous $MgSO_4$, and then concentrated under vacuum to give the crude product, which was purified by flash chromatography (eluent: ethyl acetate/hexane = 1 : 6) to afford pure compound **10** (2.587 g, 4.657 mmol) as white crystals in 89% yield. Mp 81–82 °C. $[\alpha]_D^{20}$ = −45 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.2 Hz, 2H, Ar-H in Bz), 7.85 (d, J = 7.2 Hz, 2H, Ar-H in Bz), 7.79 (d, J = 7.2 Hz, 2H, Ar-H in Bz), 7.50 (t, J = 7.2 Hz, 1H, Ar-H in Bz), 7.44–7.34 (m, 4H, Ar-H in Bz), 7.31–7.19 (m, 4H, Ar-H in Bz), 6.07 (d, J = 5.6 Hz, 1H, H-4), 5.92 (d, J = 1.9 Hz, 1H, olefinic proton, H-6), 5.78–5.56 (m, 2H, H-2 and H-3), 4.85 (d, J = 13.4 Hz, 1H, C*H*HOBz), 4.75 (dd, J = 13.4 Hz, 1H, CH*H*OBz), 4.43 (dd, J_1 = 6.0 Hz, J_2 = 1.9 Hz, 1H, H-1), 1.90 (s, 3H, CH_3 in Ac). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.87, 165.88, 165.82, 165.49, 134.66 (2C), 133.48 (2C), 133.43 (2C), 129.80 (2C), 129.78 (2C), 129.39, 128.73 (2C), 128.66 (2C), 128.56 (2C), 128.41 (2C), 125.55, 72.38, 71.89, 70.33, 63.11, 60.84, 20.58. HRMS (ESI) calcd for $C_{30}H_{25}N_3O_8Na$ [M + Na]$^+$: 578.1539; found: 578.1541. IR (KBr film) ν = 2096 (N_3), 1729 (C=O), 1451, 1276, 1094, 1069, 1025, 707 cm^{-1}.

(1*R*,2*S*,3*S*,4*R*)-1-Azido-5-benzoyloxymethyl-2,3-dibenzoyloxy-4-hydroxy-cyclohex-5-ene 11. Compound **10** (2.000 g, 3.600 mmol) was dissolved in MeOH (20 mL), and *p*-TsOH (1.240 g, 7.201 mmol) was added. After the addition was finished, the mixture was heated and stirred at reflux for approximately 3 h. When the reaction was complete (checked by TLC, eluent: eluent: ethyl acetate/hexane = 1 : 5), the solvent was evaporated under vacuum. Ethyl acetate (30 mL) and a dilute aqueous solution of potassium carbonate (1 M, 20 mL) were added. The mixture was further stirred for 5 min, and the two phases were separated. The aqueous phase was extracted again with ethyl acetate (20 mL). The organic extracts were combined, and then dried over anhydrous $MgSO_4$. The organic solution was concentrated under vacuum to give a pale-yellow oily residue which was purified by flash chromatography (eluent: ethyl acetate/hexane = 1 : 5) to afford compound **11** (1.535 g, 2.989 mmol) as white crystals in 83% yield. Mp 149–151 °C. $[\alpha]_D^{20}$ = +30 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.3 Hz, 2H, Ar-H in Bz), 7.95 (d, J = 7.3 Hz, 2H, Ar-H in Bz), 7.91 (d, J = 7.3 Hz, 2H, Ar-H in Bz), 7.59 (t, J = 7.4 Hz, 1H, Ar-H in Bz), 7.52–7.42 (m, 4H, Ar-H in Bz), 7.38–7.29 (m, 4H, Ar-H in Bz), 5.87 (d, J = 1.8 Hz, 1H, olefinic proton, H-6), 5.68 (dd, J_1 = 10.8, J_2 = 8.6 Hz, 1H, H-2), 5.55 (dd, J_1 = 10.8, J_2 = 7.4 Hz, 1H, H-3), 5.18 (d, J = 13.5 Hz, 1H, C*H*HOBz), 4.88 (d, J = 13.5 Hz, 1H, CH*H*OBz), 4.70 (d, J = 7.4 Hz, 1H, H-4), 4.47 (dd, J_1 = 8.6 Hz, J = 1.8 Hz, 1H, H-1). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.99, 166.51, 165.77, 137.59 (2C), 133.53 (2C), 133.47 (2C), 129.88 (2C), 129.83 (2C), 129.78, 129.49, 128.86, 128.77, 128.56, 128.43 (2C), 128.41 (2C), 123.37, 76.00, 71.95, 70.74, 63.65, 61.09. HRMS (ESI) calcd for $C_{28}H_{23}N_3O_7Na$ [M + Na]$^+$: 536.1434; found: 536.1429. IR (KBr film) ν = 3381 (O–H), 2105 (N_3), 1731 (C=O), 1451, 1278, 1127, 1069, 1024, 709 cm^{-1}.

(1*R*,2*S*,3*R*,4*R*)-1-Azido-5-benzoyloxymethyl-2,3-dibenzoyloxy-4-methylsulfonyloxy-cyclohex-5-ene 12. Compound **11** (1.002 g, 1.951 mmol), triethylamine (395.0 mg, 3.903 mmol) and DMAP (24.0 mg, 0.196 mmol) were dissolved in ethyl acetate (15 mL). The resulting solution was cooled down to 0 °C by an ice bath. Methanesulfonyl chloride (335.5 mg, 2.929 mmol) was then added. After the addition was finished, the reaction mixture was further stirred at 0 °C for 0.5 h. After the reaction was complete (checked by TLC, eluent: ethyl acetate/hexane = 1 : 5), a dilute aqueous solution of hydrochloric acid (1 M, 10 mL) was then added. The mixture was further stirred at room temperature for 5 min. Two phases were separated, and the aqueous phase was extracted again with ethyl acetate (20 mL). The combined extracts were washed with a dilute aqueous solution of potassium carbonate (1 M, 20 mL), and then dried over anhydrous $MgSO_4$. Evaporation of solvent under vacuum gave an off-white solid residue, which was purified by flash chromatography (eluent: ethyl acetate/hexane = 1 : 6) to give pure compound **12** (1.039 g, 1.756 mmol) as white crystals in 90% yield. Mp 139–141 °C. $[\alpha]_D^{20}$ = +43 (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 7.3 Hz, 2H, Ar-H in Bz), 7.98–7.89 (m, 4H, Ar-H in Bz), 7.60 (t, J = 7.3 Hz, 1H, Ar-H in Bz), 7.56–7.43 (m, 4H, Ar-H in Bz), 7.38–7.29 (m, 4H, Ar-H in Bz), 6.08 (d, J = 1.8 Hz, 1H, olefinic proton, H-6), 5.90–5.92 (m, 2H, H-3 and H-4), 5.69 (dd, J_1 = 10.2 Hz, J_2 = 8.5 Hz, 1H, H-2), 5.01 (d, J = 12.2 Hz, 1H, ab peak, C*H*HOBz), 4.99 (d, J = 12.2 Hz, 1H, ab peak, CH*H*OBz), 4.51 (dd, J_1 = 8.5 Hz, J_2 = 1.8 Hz, 1H, CH*H*OBz), 2.93 (s, 3H, CH_3 in Ms). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.03, 165.74, 165.48, 133.68 (2C), 133.64 (2C), 133.49 (2C), 133.16, 129.90 (2C), 129.84 (2C), 129.74, 129.35, 128.58, 128.52 (2C), 128.46 (2C), 127.58 (2C), 76.96, 71.81, 71.74, 63.17, 60.39, 38.86. HRMS (ESI) calcd for $C_{29}H_{25}N_3O_9SNa$ [M + Na]$^+$: 614.1209; found: 614.1213. IR

(neat) ν = 2104 (N_3), 1734 (C=O), 1670, 1451, 1315, 1277, 1177, 1093, 1027, 708 cm^{-1}.

(1*R*,2*S*,3*S*,4*S*)-4-Acetoxy-1-azido-5-benzoyloxymethyl-2,3-dibenzoyloxy-cyclohex-5-ene 13. Acetic acid (1.219 g, 20.30 mmol) was dissolved in toluene (10 mL), and DBU (1.545 g, 10.15 mmol) was added. The resulting solution was heated and stirred under reflux for 1 h, then cooled down to room temperature. Compound **12** (1.000 g, 1.690 mmol) was added. After the addition was finished, the reaction mixture was further stirred at 80 °C for 2 h. After the reaction was complete, the reaction mixture was cooled down to room temperature. Ethyl acetate (25 mL) and a dilute aqueous solution of hydrochloric acid (1 M, 20 mL) were added, and the mixture was vigorously stirred for 5 min. Two phases were separated, and the aqueous phase was extracted again with ethyl acetate (25 mL). The organic extracts were combined, washed with a dilute aqueous solution of potassium carbonate (2 M, 30 mL), and dried over anhydrous $MgSO_4$. Evaporation of solvent under vacuum gave a yellow liquid residue, which was purified by flash chromatography (eluent: ethyl acetate/hexane = 1 : 9) to afford compound **13** (789.0 mg, 1.420 mmol) as a colorless oil in 84% yield. $[\alpha]_D^{20}$ = +20 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.2 Hz, 2H, Ar-H in Bz), 7.90 (d, J = 7.2 Hz, 2H, Ar-H in Bz), 7.78 (d, J = 7.2 Hz, 2H, Ar-H in Bz), 7.52 (t, J = 7.2 Hz, 1H, Ar-H in Bz), 7.47–7.36 (m, 4H, Ar-H in Bz), 7.32–7.23 (m, 4H, Ar-H in Bz), 6.02 (d, J = 1.6 Hz, 1H, olefinic proton, H-6), 5.97 (d, J = 4.0 Hz, 1H, H-4), 5.88 (dd, J_1 = 11.0 Hz, J_2 = 8.4 Hz, 1H, H-2), 5.45 (dd, J_1 = 11.0, J_2 = 4.0 Hz, 1H, H-3), 4.81 (s, 2H, CH_2OBz), 4.32 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H, H-1), 1.99 (s, 3H, CH_3 in Ac). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.04, 165.87, 165.72, 165.40, 133.58 (2C), 133.50, 133.44, 129.76, 129.75, 129.61 (2C), 129.42 (2C), 128.95, 128.80, 128.57 (2C), 128.48 (2C), 128.45 (2C), 127.49 (2C), 70.11, 69.65, 65.68, 63.90, 61.19, 20.64. HRMS (ESI) calcd for $C_{30}H_{25}N_3O_8Na$ [M + Na]$^+$: 578.1539; found: 578.1534. IR (neat) ν = 2101 (N_3), 1727 (C=O), 1451, 1267, 1219, 1109, 1069, 1026, 710 cm^{-1}.

(1*R*,2*S*,3*S*,4*S*)-4-Acetoxy-5-benzoyloxymethyl-2,3-dibenzoyloxy-1-octylamino-cyclohex-5-ene 14. To a solution of compound **13** (0.600 g, 1.080 mmol) in anhydrous tetrahydrofuran (8 mL) was added triphenylphosphine (425.0 mg, 1.620 mmol), triethylamine (109.3 mg, 1.080 mmol) and octanal (415.4 mg, 3.240 mmol) in turn. The resulting solution was stirred at room temperature for 3 h. After the reaction was complete (checked by TLC, eluent: ethyl acetate/hexane = 1 : 4), the solvent was evaporated under vacuum to give an oily residue which was dissolved in methanol (8 mL). The resulting solution was cooled to 0 °C. Sodium borohydride (163.5 mg, 4.322 mmol) was then added slowly into the mixture at 0 °C. The reaction mixture was further stirred at 0 °C for 30 min. After methanol was removed by vacuum distillation, water (15 mL) and ethyl acetate (20 mL) were added, and the mixture was vigorously stirred for 5 min. The two phases were separated, and the aqueous phase was extracted again with ethyl acetate (25 mL). The organic extracts were combined and dried over anhydrous $MgSO_4$. Evaporation of solvent under vacuum gave a pale yellow liquid, which was purified by flash chromatography (eluent: ethyl acetate/hexane = 1 : 4) to afford compound **14** (561.5 mg, 0.8749 mmol) in 81% yield. $[\alpha]_D^{20}$ = +25 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.9 Hz, 2H, Ar-H in Bz), 7.96 (d, J = 7.9 Hz, 2H, Ar-H in Bz), 7.85 (d, J = 7.9 Hz, 2H, Ar-H in Bz), 7.57 (t, J = 6.8 Hz, 1H, Ar-H in Bz), 7.50–7.39 (m, 4H, Ar-H in Bz), 7.37–7.29 (m, 4H, Ar-H in Bz), 6.18 (d, J = 1.6 Hz, 1H, olefinic proton, H-6), 6.04 (d, J = 3.9 Hz, 1H, H-4), 5.85 (dd, J_1 = 10.8 Hz, J_2 = 8.2 Hz, 1H, H-2), 5.53 (dd, J_1 = 10.8 Hz, J_2 = 3.9 Hz, 1H, H-3), 4.87 (s, 2H, CH_2OBz), 3.72 (dd, J_1 = 1.6 Hz, J_2 = 8.2 Hz, 1H, H-1), 2.83–2.75 (m, 1H, NC*H*H), 2.62–2.54 (m, 1H, NCH*H*), 2.03 (s, 3H, CH_3 in Ac), 1.49–1.35 (m, 2H), 1.35–1.11 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.17, 166.37, 166.06, 165.57, 133.23 (2C), 133.18 (2C), 130.31 (2C), 129.73 (2C), 129.68 (2C), 129.67 (2C), 129.53, 128.48, 128.39 (2C), 128.35 (2C), 128.34 (2C), 70.66, 70.34, 66.39, 64.72, 58.51, 45.79, 31.78, 30.37, 29.71, 29.69, 29.68, 29.40, 27.13, 22.63, 14.07. HRMS (ESI) calcd for $C_{38}H_{43}NO_8Na$ [M + Na]$^+$: 664.2886; found: 664.2888. IR (neat) ν = 3385 (N–H), 2923, 1727 (C=O), 1451, 1268, 1110, 1069, 1027, 711 cm^{-1}.

(1*R*,2*S*,3*S*,4*S*)-5-Hydroxymethyl-1-octylamino-2,3,4-trihydroxy-cyclohex-5-ene [*N*-octyl-4-*epi*-β-valienamine] 2. Compound **14** (550.0 mg, 0.8570 mmol) was dissolved in a mixed solvent of methanol (8 mL) and ammonia hydrate (25% w/w, 2 mL), and the mixture was stirred at room temperature for approximately 24 h. The solution was then concentrated under vacuum to give an oily residue, which was dissolved in pure water (15 mL). The aqueous solution was twice washed with toluene (2 × 10 mL). The aqueous solution was concentrated to dryness under vacuum to give an oily residue, which was purified by chromatography on a column of Duolite-C20 resin (eluent: methanol/water/concentrated ammonia = 7 : 3 : 0.2) to furnish pure compound **2** (224.2 mg, 0.7801 mmol) as a colorless oil in 91% yield. $[\alpha]_D^{20}$ = +6 (*c* 1.5, MeOH) {lit.[10] $[\alpha]_D^{25}$ = +3.0 (*c* 1.0, MeOH)}. ^{1}H NMR (400 MHz, CD_3OD) δ 5.73 (d, J = 1.8 Hz, 1H, H-6), 4.18–4.10 (m, 3H, H-2, H-3 and H-4), 3.73–3.62 (m, 1H, C*H*HOH), 3.49–3.42 (m, 1H, CH*H*OH), 3.11 (dd, J_1 = 7.6 Hz, J_2 = 1.8 Hz, 1H, H-1), 2.76–2.70 (m, 1H, NC*H*H), 2.58–2.52 (m, 1H, NCH*H*), 1.60–1.44 (m, 2H), 1.44–1.17 (m, 10H), 0.90 (t, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CD_3OD) δ 140.53, 125.36, 73.84, 70.84, 68.15, 63.86, 61.77, 46.92, 33.01, 30.91, 30.62, 30.40, 28.44, 23.73, 14.48. HRMS (ESI) calcd for $C_{15}H_{29}NO_4Na$ [M + Na]$^+$: 310.1994; found: 310.1989. IR (neat) ν = 3450–3300 (O–H, N–H), 2925, 2853, 1467, 1101, 1052, 1018, 962, 621, 471 cm^{-1}.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (*a*) M. L. Schultz, L. Tecedor, M. Chang and B. L. Davidson, *Trends Neurosci.*, 2011, **34**, 401–410; (*b*) T. M. Cox and M. B. Cachon-Gonzalez, *J. Pathol.*, 2012, **226**, 241–254; (*c*) K. V. Rama Rao and T. Kielian, *Neurosci*, 2016, **323**, 195–206.
2 (*a*) R.-M. Boustany, W.-H. Qian and K. Suzuki, *Am. J. Hum. Genet.*, 1993, **53**, 881–888; (*b*) A. Caciotti, M. A. Donati,

A. Boneh, A. d'Azzo, A. Federico, R. Parini, D. Antuzzi, T. Bardelli, D. Nosi, V. Kimonis, E. Zammarchi and A. Morrone, *Hum. Mutat.*, 2005, **25**, 285–292.

3 (*a*) O. Amaral, A. Marcao, M. S. Miranda, R. J. Desnick and M. E. Grace, *Eur. J. Hum. Genet.*, 2000, **8**, 95–102; (*b*) K. Michelin, A. Wajner, L. da S. Goulart, A. A. Fachel, M. L. S. Pereira, A. S. de Mello, F. T. S. Souza, R. F. Pires, R. Giugliani and J. C. C. Coelho, *Clin. Chim. Acta*, 2004, **343**, 145–153; (*c*) R. O. Brady, J. N. Kanfer, R. M. Bradley and D. Shapiro, *J. Clin. Invest.*, 1966, **45**, 1112–1115.

4 (*a*) K. J. Valenzano, R. Khanna, A. C. Powe Jr, R. Boyd, G. Lee, J. J. Flanagan and E. R. Benjamin, *Assay Drug Dev. Technol.*, 2011, **9**, 213–235; (*b*) R. E. Boyd, G. Lee, P. Rybczynski, E. R. Benjamin, R. Khanna, B. A. Wustman and K. J. Valenzano, *J. Med. Chem.*, 2013, **56**, 2705–2725.

5 H. Suzuki, U. Ohto, K. Higaki, T. Mena-Barragan, M. Aguilar-Moncayo, C. O. Mellet, E. Nanba, J. M. G. Fernandez, Y. Suzuki and T. Shimizu, *J. Biol. Chem.*, 2014, **289**, 14560–14568.

6 A. R. Sawkar, W. C. Cheng, E. Beutler, C. H. Wong, W. E. Balch and J. W. Kelly, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 15428–15433.

7 (*a*) H. Lin, Y. Sugimoto, Y. Ohsaki, H. Ninomiya, A. Oka, M. Taniguchi, H. Ida, Y. Eto, S. Ogawa, Y. Matsuzaki, M. Sawa, T. Inoue, K. Higaki, E. Nanba, K. Ohno and Y. Suzuki, *Biochim. Biophys. Acta*, 2004, **1689**, 219–228; (*b*) K. Lei, H. Ninomiya, M. Suzuki, T. Inoue, M. Sawa, M. Iida, H. Ida, Y. Eto, S. Ogawa, K. Ohno and Y. Suzuki, *Biochim. Biophys. Acta*, 2007, **1772**, 587–596; (*c*) H. Jo, K. Yugi, S. Ogawa, Y. Suzuki and Y. Sakakibara, *J. Proteomics Bioinf.*, 2010, **3**, 104–112; (*d*) Z. Luan, L. Li, H. Ninomiya, K. Ohno, S. Ogawa, T. Kubo, M. Iida and Y. Suzuki, *Blood Cells, Mol., Dis.*, 2010, **44**, 48–54.

8 (*a*) Y. Suzuki, *J. Inherited Metab. Dis.*, 2006, **29**, 471–476; (*b*) Y. Suzuki, *Cell. Mol. Life Sci.*, 2008, **65**, 351–353; (*c*) K. Higaki, L. Li, U. Bahrudin, S. Okuzawa, A. Takamuram, K. Yamamoto, K. Adachi, R. C. Paraguison, T. Takai, H. Ikehata, L. Tominaga, I. Hisatome, M. Iida, S. Ogawa, J. Matsuda, H. Ninomiya, Y. Sakakibara, K. Ohno, Y. Suzuki and E. Nanba, *Hum. Mutat.*, 2011, **32**, 843–852; (*d*) Y. Suzuki, S. Ichinomiya, M. Kurosawa, J. Matsuda, S. Ogawa, M. Iida, T. Kubo, M. Tabe, M. Itoh, K. Higaki, E. Nanba and K. Ohno, *Mol. Genet. Metab.*, 2012, **106**, 92–98; (*e*) M. A. Hossain, K. Higaki, M. Shinpo, E. Nanba, Y. Suzuki, K. Ozono and N. Sakai, *Brain Dev.*, 2016, **38**, 175–180.

9 S. Ogawa, M. Ashiura, C. Uchida, S. Watanabe, C. Yamazaki, K. Yamagishi and J.-i. Inokuchi, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 929–932.

10 S. Kuno, A. Takahashi and S. Ogawa, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 7189–7192.

11 S. Ogawa, Y. K. Matsunaga and Y. Suzuki, *Bioorg. Med. Chem.*, 2002, **10**, 1967–1972.

12 S. Kuno, A. Takahashi and S. Ogawa, *Carbohydr. Res.*, 2013, **368**, 8–15.

13 S. Ogawa, Y. Iwasawa, T. Nose, T. Suami, S. Ohba, M. Ito and Y. Saito, *J. Chem. Soc., Perkin Trans. 1*, 1985, 904–906.

14 (*a*) Y. Suzuki, S. Ogawa and Y. Sakakibara, *Perspect. Med. Chem.*, 2009, **3**, 7–19; (*b*) S. Ogawa, M. Kanto and Y. Suzuki, *Mini-Rev. Med. Chem.*, 2007, **7**, 679–691; and the references cited therein.

15 (*a*) L. B. Enrich, M. L. Scheuermann, A. Mohadjer, K. R. Matthias, C. F. Eller, M. S. Newman, M. Fujinaka and T. Poon, *Tetrahedron Lett.*, 2008, **49**, 2503–2505; (*b*) R. H. Sui, *Chem. Eng. Technol.*, 2008, **31**, 469–473; (*c*) L. Z. Dang, G. H. Li, Z. S. Yang, S. L. Luo, X. Zheng and K. Q. Zhang, *Ann. Microbiol.*, 2010, **60**, 317–320; (*d*) T. Usuki, N. Yasuda, M. Yoshizawa-Fujita and M. Rikukawa, *Chem. Commun.*, 2011, **47**, 10560–10562; (*e*) D. V. Bochkov, S. V. Sysolyatin, A. I. Kalashnikov and I. A. Surmacheva, *J. Chem. Biol.*, 2012, **5**, 5–17; (*f*) E. Scalabrin, M. Radaelli and G. Capodaglio, *Plant Physiol. Biochem.*, 2016, **103**, 53–60.

16 (*a*) M. Kramer, J. Bongaerts, R. Bovenberg, S. Kremer, U. Müller, S. Orf, M. Wubbolts and L. Raeven, *Metab. Eng.*, 2003, **5**, 277–283; (*b*) S. Ghosh, Y. Chisti and U. C. Banerjee, *Biotechnol. Adv.*, 2012, **30**, 1425–1431.

17 (*a*) B. A. Bohm, *Chem. Rev.*, 1965, **65**, 435–466; (*b*) S. Jiang and G. Singh, *Tetrahedron*, 1998, **54**, 4697–4753.

18 (*a*) B. Avula, Y.-H. Wang, T. J. Smillie and I. A. Khan, *Chromatographia*, 2009, **69**, 307–314; (*b*) J. Just, B. J. Deans, W. J. Olivier, B. Paull, A. C. Bissember and J. A. Smith, *Org. Lett.*, 2015, **17**, 2428–2430.

19 (*a*) N. R. Candeias, B. Assoah and S. P. Simeonov, *Chem. Rev.*, 2018, **118**, 10458–10550; (*b*) J. C. Borah, *Curr. Sci.*, 2015, **109**, 1672–1679; (*c*) G. Rawat, P. Tripathi and R. K. Saxena, *Appl. Microbiol. Biotechnol.*, 2013, **97**, 4277–4287; (*d*) A. M. Estevez and R. J. Estevez, *Mini-Rev. Med. Chem.*, 2012, **12**, 1443–1454.

20 (*a*) L. D. Nie, X. X. Shi, K. H. Ko and W. D. Lu, *J. Org. Chem.*, 2009, **74**, 3970–3973; (*b*) L.-D. Nie and X.-X. Shi, *Tetrahedron: Asymmetry*, 2009, **20**, 124–129; (*c*) L.-D. Nie, X.-X. Shi, N. Quan, F.-F. Wang and X. Lu, *Tetrahedron: Asymmetry*, 2011, **22**, 1692–1699; (*d*) L.-D. Nie, W. Ding, X.-X. Shi, N. Quan and X. Lu, *Tetrahedron: Asymmetry*, 2012, **23**, 742–747; (*e*) N. Quan, L.-D. Nie, X.-X. Shi, R.-H. Zhu and X. Lu, *Chin. J. Chem.*, 2012, **30**, 2759–2766; (*f*) L.-D. Nie, F.-F. Wang, W. Ding, X.-X. Shi and X. Lu, *Tetrahedron: Asymmetry*, 2013, **24**, 638–642; (*g*) W. Ding, J.-P. Yu, X.-X. Shi, L.-D. Nie, N. Quan and F.-L. Li, *Tetrahedron: Asymmetry*, 2015, **26**, 1037–1042; (*h*) W. Zhang, X.-L. Zhu, W. Ding and X.-X. Shi, *Tetrahedron: Asymmetry*, 2015, **26**, 1375–1381; (*i*) F.-L. Li, W. Ding, N. Quan, J.-J. Wu, Y.-G. He, X.-L. Zhu, X.-X. Shi and J.-H. Zhao, *Chin. J. Chem.*, 2017, **35**, 457–464.

21 N. Quan, L.-D. Nie, R.-H. Zhu, X.-X. Shi, W. Ding and X. Lu, *Eur. J. Org. Chem.*, 2013, 6389–6396.

22 T. K. M. Shing, V. W.-F. Tai and E. K. W. Tam, *Angew. Chem., Int. Ed.*, 1994, **33**, 2312–2313.

23 B. Plietker and M. Niggemann, *Org. Lett.*, 2003, **5**, 3353–3356.

24 (*a*) J. Li, H.-N. Chen, H. W. Chang, J. H. Wang and C.-W. T. Chang, *Org. Lett.*, 2005, **7**, 3061–3064; (*b*) H. Chen, J. P. Zhao, Y. N. Li, F. J. Shen, X. L. Li, Q. M. Yin, Z. B. Qin, X. H. Yan, Y. F. Wang, P. Z. Zhang and J. C. Zhang, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 574–576.

25 X.-X. Shi, C.-L. Shen, J.-Z. Yao, L.-D. Nie and N. Quan, *Tetrahedron: Asymmetry*, 2010, **21**, 277–284.

