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

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$N$-Octyl-$\beta$-valienamine (NOV) 1 and $N$-octyl-4-epi-$\beta$-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 $\beta$-galactosidase and $\beta$-glucosidase, respectively.2,4 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-$\beta$-valienamine (NOV) 1 (Fig. 1) could be used as a potent chemical chaperone for the treatment of Gaucher disease by stabilizing $\beta$-glucosidase,2 and $N$-octyl-4-epi-$\beta$-valienamine (NOEV) 2 (see Fig. 1) could be used as a potent chemical chaperone for treatment of $G_{M1}$-gangliosidosis by stabilizing $\beta$-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 $\beta$-valienamine by Ogawa et al. in 1996.9 NOV 1 was also synthesized from (−)-vibocurciquitol by Kuno et al. in 2011.10 NOEV 2 was first synthesized from NOV 1 by Ogawa et al. in 200211 via chiral alcohol epimerization at the C-4 position through an oxidation–reduction sequence. NOEV 2 was also synthesized from (−)-proto-vibocurciquitol by Kuno et al. in 2011.10 An improved concise synthesis of NOEV 2 from (−)-proto-vibocurciquitol 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)(−)-x-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 processes16 and chemical syntheses.17 It is noted that (−)-shikimic acid is particularly abundant in Chinese star anise (Illicium verum),15c,18 and thus can be readily manufactured in a large quantity by extraction from the Chinese star anise.14b (−)-Shikimic acid has captured worldwide attention 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 pharmacologically valuable molecules from (−)-shikimic acid.19 To continue our research programs, we have just studied highly stereoselective, efficient and practical syntheses of NOV 1 and NOEV 2 by using...
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 (SOCl₂) 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 of compound 7 with 1.5 equivalents of triphenylphosphine at room temperature in anhydrous tetrahydrofuran provided anaza-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 (NaBH₄) 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 (CH₃OH/NH₃·H₂O, 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 (Ac₂O), 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 (SOCl₂) and 3.0 equivalents of pyridine (Py) under reflux (41 °C) in CH₂Cl₂, regioselective elimination occurred smoothly to furnish an
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,23 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 reduction24 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 (AcOH/TsOH) under reflux in dichloromethane (300 mL), and a catalytic amount of DMAP at 0 °C in ethyl acetate, methanesulfonate 12 was thus obtained in 90% yield. Accordingly to a known method,23 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.

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 13C 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.23

### 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
for 2 h and filtered by suction, the filter cake was washed with anhydrous methanol (2 x 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. Et3N (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 K2CO3 (10% w/w, 100 mL) and brine (20 mL). The organic solution was then dried over anhydrous MgSO4. 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. [α]D20 = +103 (c 0.9, CHCl3) 1H NMR (400 MHz, CDCl3) 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), 7.95-7.90 (m, 2H, H-2 and H-3), 7.57 (dd, J = 10.5, J = 7.6 Hz, 1H, H-4), 4.83 (d, J = 13.6 Hz, 1H, CHOBz), 4.81 (d, J = 13.6 Hz, 1H, CHOBz), 4.11-4.04 (m, 1H, H-5), 2.73 (dd, J = 17.6 Hz, J = 5.8 Hz, 1H, H-6), 2.47 (dd, J = 17.5 Hz, J = 10.1 Hz, 1H, the other H-6). 13C NMR (100 MHz, CDCl3) δ 166.07, 166.05, 165.68, 134.29, 134.35, 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) calcld for C28H23N3O6Na [M + Na]+: 554.1539; found: 554.1544. IR (KBr film) ν = 3446 (O-H), 2094 (N3), 1731 (C=O), 1451, 1275, 1116, 1068, 1025, 708 cm−1.

(1R,2S,3S,4S,5S)-1-Azido-5-benzoyloxymethyl-2,3,4-triiodobenzoyloxy-4,5-dihydroxycyclohexane 6. A solution of compound 5 (3.00 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 benzyl 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 x 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 MgSO4. 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. [α]D20 = +29 (c 0.8, CHCl3). 1H NMR (400 MHz, CDCl3) 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 = 10.0 Hz, J = 10.01 Hz, 1H, H-3), 5.63 (d, J = 10.0 Hz, 1H, H-4), 5.54 (dd, J = 10.1 Hz, J = 9.9 Hz, 1H, H-2), 4.38 (d, J = 11.6 Hz, 1H, CHOBz), 4.27-4.20 (m, 1H, H-1), 4.18 (d, J = 11.6 Hz, 1H, CHOBz), 2.38 (dd, J = 14.2 Hz, J = 4.7 Hz, 1H, H-6), 1.91 (dd, J = 14.2 Hz, J = 11.0 Hz, 1H, the other H-6). 13C NMR (100 MHz, CDCl3) δ 7.66, 166.35, 165.93, 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) calcld for C34H23I3NO8Na [M + Na]+: 658.1901; found: 658.1806. IR (KBr film) ν = 3503 (O-H), 2107 (N3), 1734 (C=O), 1451, 1319, 1266, 1096, 1068, 1027, 708 cm−1.

(1R,2S,3S,4R)-1-Azido-5-benzoyloxymethyl-2,3,4-triiodobenzoyloxy-cyclohex-5-ene 7. Compound 6 (2.000 g, 3.146 mmol) was dissolved in CH2Cl2 (25 mL), then the resulting solution was cooled down to 0 °C by an ice bath. SOC12 (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 MgSO4, 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. [α]D20 = −65 (c 0.9, CHCl3). 1H NMR (400 MHz, CDCl3) 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), 7.82 (d, J = 7.5 Hz, 2H, Ar-H in Bz), 7.81 (d, J = 7.5 Hz, 2H, Ar-H in Bz), 7.59–7.46 (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, J1 = 10.5 Hz, J2 = 7.4 Hz, 1H, H-3), 5.81 (dd, J1 = 10.5 Hz, J2 = 8.2 Hz, 1H, H-2), 4.94 (d, J = 12.0 Hz, 1H, ab peak, CH2OHb), 4.92 (d, J = 12.0 Hz, 1H, ab peak, CH2OHb), 4.57 (dd, J1 = 8.2 Hz, J2 = 1.9 Hz, 1H, H-1), 3.08 (s, 3H, Me3Si). 13C NMR (100 MHz, CDCl3) δ 165.82, 165.73, 165.63, 165.53, 134.81, 133.30, 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) calcld for C16H25NO3Na [M + Na]+: 360.1696; found: 360.1697. IR (KBr film) ν = 2104 (N3), 1720 (C=O), 1515, 1315, 1264, 1094, 1068, 1025, 708 cm⁻¹.

(1R,2S,3,5R)-5-Benzoyloxymethyl-1-octylamo-2,3,4-trihydroxy-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 MgSO4. 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. [α]D20 = −36 (c 0.6, CHCl3). 1H NMR (400 MHz, CDCl3) 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, J1 = 10.3 Hz, J2 = 7.4 Hz, 1H, H-3), 5.73 (dd, J1 = 10.3 Hz, J2 = 8.0 Hz, 1H, H-2), 4.91 (d, J = 11.8 Hz, 1H, ab peak, CH2OHb), 4.89 (d, J = 11.8 Hz, 1H, ab peak, CH2OHb), 3.91 (d, J = 8.0 Hz, J2 = 1.9 Hz, 1H, H-1), 2.84–2.77 (m, 1H, NCHH), 2.62–2.56 (m, 1H, NCHH), 1.47–1.41 (m, 2H, CH2), 1.23 (m, 1OH, (CH2)3), 0.86 (t, J = 6.9 Hz, 3H, CH3). 13C NMR (100 MHz, CDCl3) 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, 123.88 (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) calcld for C16H25NO3Na [M + Na]+: 376.3043; found: 376.3045. IR (neat) ν = 3380 (N–H), 2926, 1728 (C=O), 1601, 1523, 1451, 1314, 1266, 1106, 1069, 1026, 709 cm⁻¹.

(1R,2S,3,5R)-4-Hydroxy-methyl-1-octylamo-2,3,4-trihydroxy-cyclohex-5-ene 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 MgSO4. 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. [α]D20 = +74 (c 1.0, CHCl3). 1H NMR (400 MHz, CDCl3) 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, J1 = 10.0 Hz, J2 = 10.01 Hz, 1H, H-1), 5.56 (dd, J1 = 10.0 Hz, J2 = 9.9 Hz, 1H, H-2), 5.51 (dd, J1 = 10.1 Hz, 1H, H-4), 4.38 (dd, J1 = 11.4 Hz, 1H, CHOBz), 4.31–4.24 (m, 1H, H-1), 4.25 (dd, J1 = 11.4 Hz, 1H, CHOBz), 2.43 (dd, J1 = 14.1 Hz, J2 = 4.6 Hz, 1H, H-6), 1.98 (dd, J1 = 14.1 Hz, J2 = 11.2 Hz, 1H, the other H-6), 1.88 (s, 3H, CH3 in Ac). 13C NMR (100 MHz, CDCl3) δ 169.33, 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, 70.63, 60.39, 38.86. HRMS (ESI) caleld for C20H15N4O6Na [M + Na]+: 578.1539; found: 578.1541. IR (KBr film) v = 3381 (O–H), 2104 (N–O), 1731 (C=O), 1451, 1270, 1108, 1070, 702, 709 cm⁻¹.

(1R,2S,3S,4R)-4-Acetoxy-1-azido-5-benzoyloxyethyl-2,3-dibenzoyloxy-cyclohex-5-ene 10. Compound 9 (3.000 g, 5.231 mmol) was dissolved in CH2Cl2 (30 mL), then the resulting solution was cooled down to 0 °C by an ice bath. SOCl2 (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 MgSO4, 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. [α]D° = −45 (c 1.0, CHCL3). 1H NMR (400 MHz, CDCl3) 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, CHHOBz), 4.75 (dd, J = 13.4 Hz, 1H, CHHOBz), 4.43 (dd, J1 = 6.0 Hz, J2 = 1.9 Hz, 1H, H-1), 1.90 (s, 3H, CH3 in Ac). 13C NMR (100 MHz, CDCl3) 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, 63.31, 60.84, 20.58. HRMS (ESI) caleld for C30H27N3O9Na [M + Na]+: 596.1645; found: 596.1650. IR (KBr film) v = 3462 (O–H), 2104 (N–O), 1729 (C=O), 1451, 1270, 1108, 1070, 702, 709 cm⁻¹.
(neat) \( v = 2104 \text{ (N\textsubscript{2}), } 1734 \text{ (C=O), } 1670, 1451, 1315, 1277, 1177, 1093, 1027, 708 \text{ cm}^{-1} \).  

\( \text{(1R,2S,3S,4S)-4-Acetoxy-1-azido-5-benzoxymethyl-2,3-dibenzoyloxy-cyclohex-5-ene 13.} \) 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.  

\[ \text{MS (ESI): } m/z = 578.1539; \text{ found: } 578.1534. \]  

IR (neat) \( \text{ν(C=O)} = 1707, 1606, 1577, 1540, 1343, 1284, 1197, 1109, 1069, 1026, 710 \text{ cm}^{-1} \). 

\( \text{(1R,2S,3S,4S)-4-Acetoxy-5-benzoxymethyl-2,3-dibenzoxoyloxy-1-octylamino-cyclohex-5-ene 14.} \) To a solution of compound 13 (600.0 g, 1.080 mmol) in anhydrous tetrahydrofuran (8 mL) was added triphenylphosphine (425.0 g, 1.620 mmol), triethylamine (109.3 g, 1.080 mmol) and octanol (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 heated and stirred under reflux for 1 h. The reaction mixture was further stirred at 80 °C for 2 h. 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. The two phases were separated, and the aqueous phase was extracted again with ethyl acetate (25 mL). The organic extracts were combined, 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. 

\[ \text{MS (ESI): } m/z = 530.1994; \text{ found: } 530.1989. \]  

IR (neat) \( \text{ν(C=O)} = 1707, 1606, 1577, 1540, 1343, 1284, 1197, 1109, 1069, 1026, 710 \text{ cm}^{-1} \).

**Conflicts of interest**

There are no conflicts to declare.

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**Notes and references**

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