Synthesis of a New Cerebroside Isolated from *Typhonium giganteum* Engl†

CHEN, Xue-Song[a,b](陈雪松) WU, Yu-Lin*,[a](吴毓林) CHEN, Di-Hua*,[b](陈迪华)

[a] *State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

[b] *Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100094, China*

The stereoselecfive synthesis of typhoniside, a new cerebroside isolated from *Typhonium giganteum* Engl. was accomplished. Cerebrosides are a kind of glycolipids highly enriched on the surface of myelin-producing cells and are composed by C18-4, 8-sphingadienine, α-hydroxy acid and a saccharide head. It was the first time that cerebrosides were isolated from this traditional Chinese medicine (TCM) by us. In this paper, C18-4, 8-sphingadienine was synthesized from D-xylose via a S_N2 type reaction. α-Hydroxy acid was prepared from (*R*)-4-hydroxytetrahydrofuran-2-one, which in turn could be obtained from *L*-ascorbic acid.

Keywords *Typhonium giganteum* Engl., natural product, cerebroside, chiron approach, synthesis

Introduction

Cerebrosides are a kind of glycosphingolipids built by a long chain aminoalcohol known as a sphingoid base or long-chain base (LCB), a fatty acid residue and a saccharide head.[1] They are important surface molecules found in virtually all cells. An increasing number of cerebrosides have been isolated, until now, mainly from organ tissues of higher animals, plants, marine sponges and fungi.[2] With some cerebrosides being characterized, their significant biological activities have been reported.[3] GalCer was identified as essential component of the neural receptor for type 1 human immunodeficiency virus (HIV) surface glycoprotein gp120.[3a] In 1998, Holleran *et al*.[3b] reported that glucosylceramides stimulate mitogenesis in aged marine Epidermis. Futerman[3c] demonstrated that ongoing synthesis of glucosylceramide is a prerequisite for both basic fibroblast growth factor (bFGF) and laminin to stimulate axon growth. The prerequisite that ceramide must be metabolized to GluCer to sustain growth was supported by contrasting observations on using stereoisomeric ceramides. The biological activities demonstrated by these compounds themselves or as components of larger structures have recently stimulated the search for more cerebrosides from natural sources or synthetic methods.

Although cerebrosides can be got from the natural sources, it is scarce and difficult to separate them into individual component. So, a number of synthetic routes about the cerebrosides[4] and its analogs[5] have been reported. Following our first time isolation and characterization cerebrosides from *Typhonium giganteum* Engl.,[6] we attempted to synthesize a representative of these new cerebrosides. Herein, a facile and convergent approach for the synthesis of such representative——Typhoniside A (**1**) is reported. This synthesis also intended to confirm its structure further and open another way providing cerebrosides for biological investigation.

Based on the retrosynthetic analysis depicted in Scheme 1, molecule **1** was divided into three fragments. Try to find a general, efficient and regioselective method for the synthesis of sphingosine or sphingadienine fragment[7] presents a major challenge for the detail synthesis of ceramide and cerebrosides. In our synthetic route, sphingadiene fragment **2** was synthesized from *D*-xylose via a S_N2' type of reaction mediated by a thioether carbanion as in our previous mentioned method.[8] Chirally pure fatty acid part **3**, (*R*)-α-hydroxydocosanoyl acid, was prepared from (*R*)-4-hydroxytetrahydrofuran-2-one, which in turn could be obtained from *L*-ascorbic acid.[9] The synthesis from **4** to **3** is shown in Scheme 2.

Treatment of (*R*)-4-hydroxy-tetrahydrofuran-2-one (**4**)[9] with a catalytic amounts (20 mol%) of trimethylsilyl trifluoromethanesulfonate (TMSOTf) and 1.5 equivalents of benzyl trichloroacetimidate prepared by sodium hydride catalyzed addition of benzyl alcohol to trichloroacetonitrile[10] yielded **5**, $[\alpha]_D^{20}$ + 35.9 (*c* 0.6, CH_2Cl_2). Lactone **5** was converted to hemiacetal **6** by DIBAL-H reduction.

* E-mail: ylwu@mail.sioc.ac.cn; dhchen99@hotmail.com

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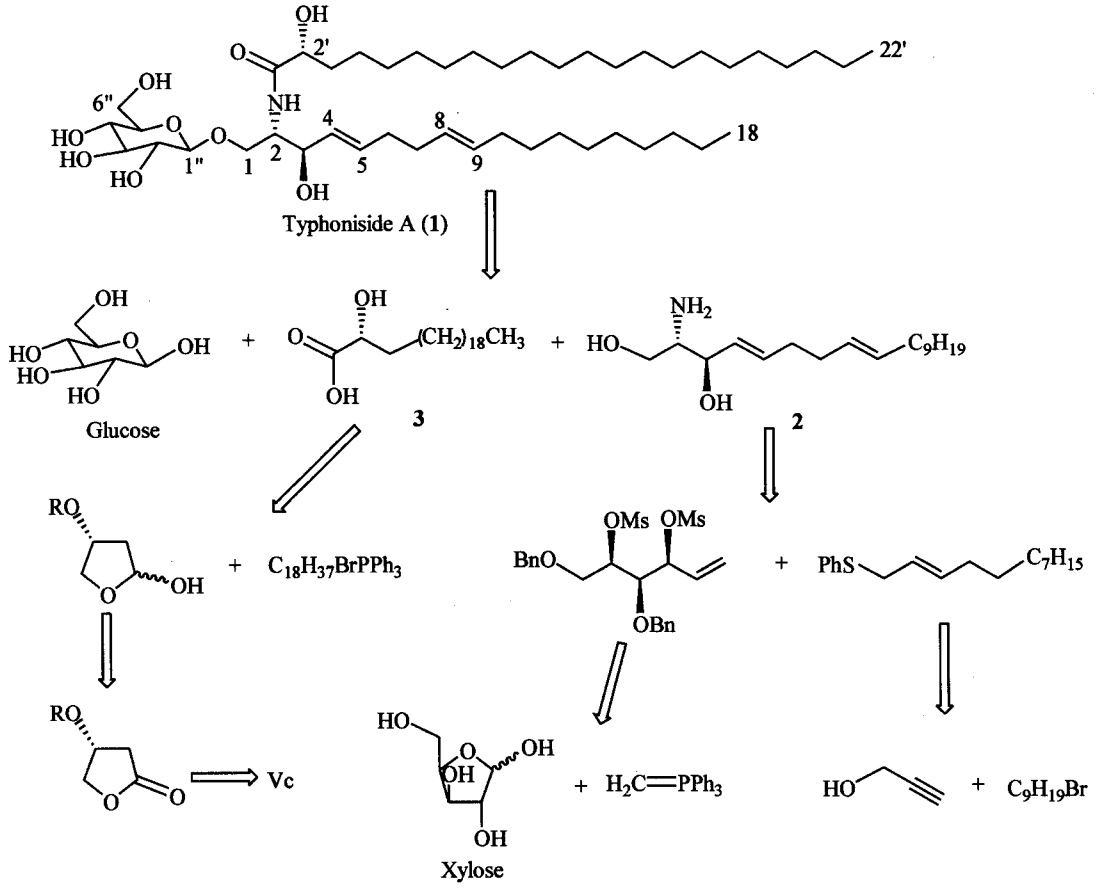
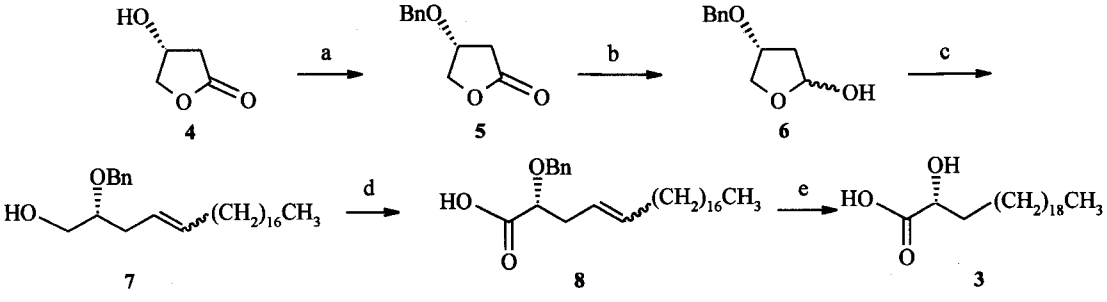
†Dedicated to Professor ZHOU Wei-Shan on the occasion of his 80th birthday, and in recognition of his contributions to organic chemistry.

Scheme 1 Retrosynthetic analysis of Typhoniside A (**1**)



Scheme 2



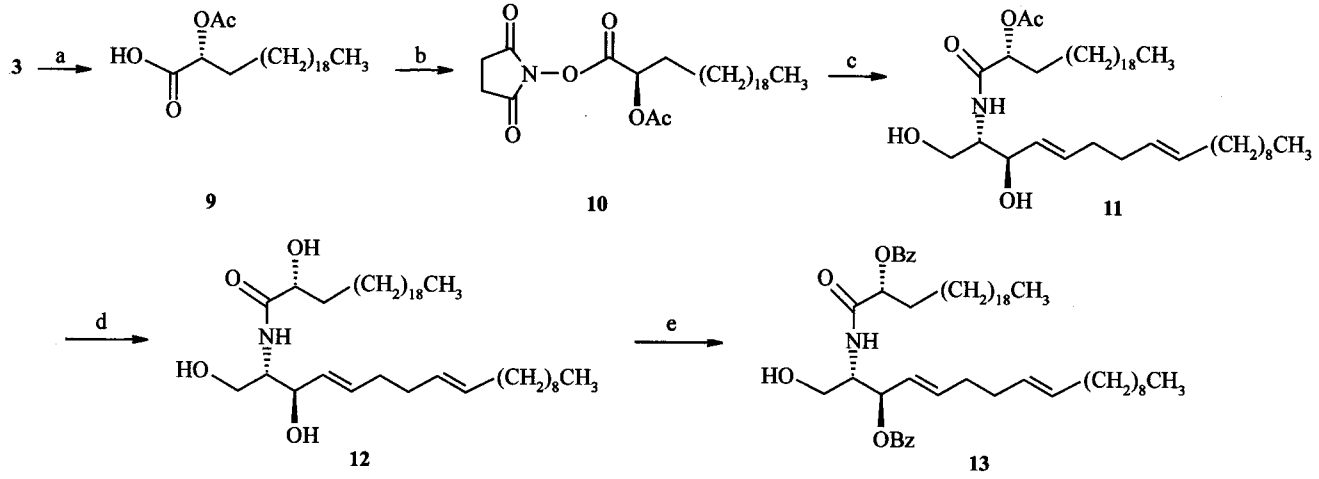
Reagents and conditions: (a) Benzyl trichloroacetimidate, TMSOTf, cyclohexane:CH_2Cl_2 (2:1), 71%; (b) DIBAL-H, CH_2Cl_2, 74%; (c) BuLi, $C_{18}H_{37}PPh_3Br$, THF, 0 ℃, 95%; (d) PDC, DMF, r.t. 32 h, 68%; (e) 10% Pd/C, cyclohexane:EtOH (1:2), 40 ℃, 20 h, 88%.

The Wittig reagent generated from the octadecanyl bromide phosphonium salt reacted with hemiacetal **6** to give alcohol **7**, which was oxidized to afford acid **8**. Removal of the benzyl protecting group and hydrogenation of the double bond gave **3**, $[\alpha]_D^{20}$ + 12 (*c* 0.93, pyridine).

Thereafter ceramide **12** was synthesized as shown in Scheme 3. Acetylation of **3** with Ac_2O yielded **9**, $[\alpha]_D^{20}$ +6.6 (*c* 0.5, $CHCl_3$).[11] Acid **9** was treated with *N*-hydroxyl succinimide in the presence of DCC to give amide **10**, which was reacted with sphingadiene **2** in the presence of DMAP and Et_3N to yield **11**, $[\alpha]_D^{20}$ +10.7 (*c* 0.5, $CHCl_3$). Removal of the protecting group with K_2CO_3 gave ceramide **12**. The ceramide **12** was converted to the glycosyl accepter **13**, $[\alpha]_D^{20}$ +6.6 (*c* 0.5, $CHCl_3$), using the conventional method (the secondary hydroxy groups of **12** were protected as benzoyl esters except for the primary hydroxy group)[4a] in 77% overall yield.

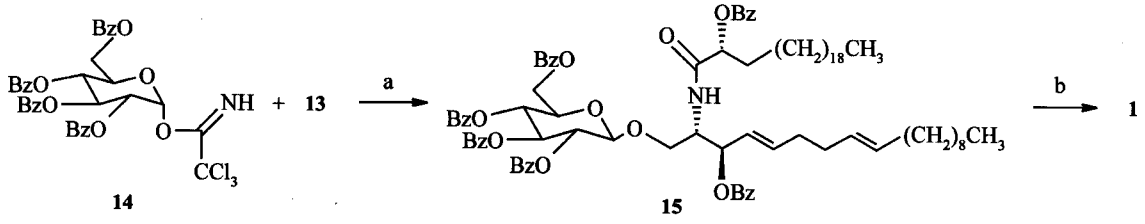
The final glycosylation was performed in the usual way. Thus ceramide **13** was treated with 2,3,4,6-tetra-*O*-benzoyl-*α*-*D*-glucopyranosyl trichloroacetimidate (**14**)[12] in the presence of a catalytic amount of TMSOTf (0.05 equiv.) in CH_2Cl_2 to provide the 1-*O*-glucosylated ceramide product **15**, $[\alpha]_D^{20}$ +20.8 (*c* 1.3, $CHCl_3$). Deprotection of the benzoyl groups in **15** yielded **1**, $[\alpha]_D^{20}$ +4.0 (*c* 0.28, $CHCl_3$:MeOH, 1:1). By comparison of the chromatographic behavior and spectroscopic data of the synthetic **1** with those of the isolated natural material,[6b] it showed a good coincidence and confirmed the structure of **1** (Table 1).

Scheme 3



Reagents and conditions: (a) $(Ac)_2O$, DMAP, CH_2Cl_2, pyridine, r.t. overnight, 100%; (b) DCC, CH_2Cl_2, 5 h, 80%; (c) **2**, DMAP, Et_3N, THF, 8 h, 95%; (d) K_2CO_3, MeOH, 90%; (e) i. TrCl, pyridine, DMAP, 80 ℃; ii. BzCl, pyridine, 14 h; iii. *p*-TsOH, CH_2Cl_2 :MeOH (2:1) 8 h, 77% in three steps.

Scheme 4



Reagents and conditions: (a) TMSOTf, CH_2Cl_2, 65%; (b) NaOMe, MeOH 80%.

In conclusion, we have accomplished a fully chiron approach synthesis of the new cerebroside——Typhoniside A (**1**) from protected *D*-glucose, (*R*)-hydroxy fatty acid prepared from *L*-ascorbic acid and sphingadienine prepared from *D*-xylose in this laboratory before.

Experimental

General

Solvents were distilled prior to use. Reactions requiring anhydrous conditions were conducted in a flame-dried, round-bottom flask, sealed with a rubber septum under reduced atmosphere of nitrogen. Evaporation of solvents was performed under reduced pressure using a rotary evaporator, with an external bath temperature of 45 ℃. Flash column chromatography was performed on silica gel H (10—40 μm, Qingdao Marine Chemical Co. China).

Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 Autopol polarimeter. IR spectra were recorded on a Perkin-Elmer 983 or Shimadzu IR-440 spectrometer. ^1H and ^{13}C NMR were recorded in $CDCl_3$ on a EM-360A, FX90Q, AMX-300, DPX-300 or DRX-400 spectrometer with TMS as the internal standard. Mass spectra were taken on a Mariner (PE, for ESI), HP5973N or HP5989A instrument. Elemental analyses were performed by the Microanalytic Laboratory of Shanghai Institute of Organic Chemistry.

(3*R*)-3-*Benzyloxy*-4-*butanolide* (**5**)

A solution of benzyl trichloroacetimidate (1.9 g, 7.5 mmol) in cyclohexane/CH_2Cl_2 mixture (8 mL, 2:1) was added to a solution of **4** (0.49 g, 4.75 mmol) in cyclohexane/CH_2Cl_2 mixture (25 mL, 2:1). The reaction mixture was stirred at room temperature for 1 h, then TMSOTf (0.16 mL) was added at 0 ℃ to the vigorously stirred mixture. Stirring was continued at room temperature for 2 h, then the resulting precipitate was filtered off through a cotton plug. The filtrate was washed with aqueous saturated $NaHCO_3$, water and then dried (Na_2SO_4), filtered, concentrated *in vacuo*. The residue was chromatographed on silica gel (petroleum ether : AcOEt, 4 : 1) to give **5** (0.65 g, 78%): TLC, R_f = 0.25 (petroleum ether : AcOEt, 4:1); $[\alpha]_D^{20}$ + 35.9 (*c* 0.5, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.25—7.35 (m, 5H, Ph), 4.05 (s, 2H, $PHCH_2$), 4.32—4.34 (m, 3H, H_3, H_4), 2.65 (s-like, 2H, H_2); IR (film) ν: 1796, 1474, 1411, 1300, 1171, 1050, 750, 702 cm^{-1}; MS(EI) *m/z* (rel. int.): 192 (M^+, 6), 164 (6), 77 (7), 104 (7), 107 (13), 92 (13), 65 (14), 91 (100). HRMS calcd for $C_{11}H_{12}O_3$ 192.07864, found 192.07753.

Table 1 NMR data of the synthetic Typhoniside **1** and the isolated natural product (500 MHz for ^1H in C_5D_5N)

Position	δ_H	
	Isolated natural product	Synthetic compound
1	4.70 (dd, J = 10.3, 5.8 Hz, 1H)	4.70 (dd, J = 10.3, 5.8 Hz, 1H)
	4.25 (dd, J = 10.3, 4.0 Hz, 1H)	4.22 (dd, J = 10.3, 4.0 Hz, 1H)
2	4.80—4.82 (m, 1H)	4.80—4.82 (m, 1H)
3	4.76 (t, J = 6.1 Hz, 1H)	4.74 (t, J = 6.1 Hz, 1H)
4	5.93 (dd, J = 15.3, 6.1 Hz, 1H)	5.93 (dd, J = 15.0, 6.1 Hz, 1H)
5	6.00 (dt, J = 15.3, 5.3 Hz, 1H)	6.00 (dt, J = 15.0, 5.3 Hz, 1H)
6	2.16—2.20 (s-like, 2H)	2.16—2.20 (s-like, 2H)
7	2.01—2.06 (s-like, 2H)	2.01—1.06 (s-like, 2H)
8	5.49 (s-like, 1H)	5.49 (s-like, 1H)
9	5.49 (s-like, 1H)	5.49 (s-like, 1H)
10	2.16—2.20 (m, 2H)	2.16—2.20 (m, 2H)
11—15	1.25—1.30 (s-like, 10H)	1.25—1.30 (s-like, 10H)
16	1.25—1.30 (s-like, 2H)	1.25—1.30 (s-like, 2H)
17	1.25—1.30 (s-like, 2H)	1.25—1.30 (s-like, 2H)
18	0.86 (t, J = 6.0 Hz, 3H)	0.86 (t, J = 7.0 Hz, 3H)
1′		
2′	4.57 (dd, J = 7.7, 3.6 Hz, 1H)	4.52 (dd, J = 7.7, 3.6 Hz, 1H)
3′	2.04—2.08 (s-like, 2H)	2.04—2.08 (s-like, 2H)
4′	1.78—1.80 (m, 2H)	1.78—1.80 (m, 2H)
5′—19′	1.25—1.30 (s-like, 30H)	1.25—1.30 (s-like, 30H)
20′	1.25—1.30 (s-like, 2H)	1.25—1.30 (s-like, 2H)
21′	1.25—1.30 (s-like, 2H)	1.25—1.30 (s-like, 2H)
22′	0.86 (t, J = 6.0 Hz, 3H)	0.86 (t, J = 7.0 Hz, 3H)
1″	4.91 (d, J = 7.7 Hz, 1H)	4.91 (d, J = 8.0 Hz, 1H)
2″	4.03 (t, J = 7.7 Hz, 1H)	3.98 (t, J = 7.7 Hz, 1H)
3″	4.23—4.25 (m, 1H)	4.22—4.24 (m, 1H)
4″	4.21—4.23 (m, 1H)	4.21—4.23 (m, 1H)
5″	3.90—3.91 (m, 1H)	3.90—3.91 (m, 1H)
6″	4.52 (dd, J = 12.0, 1.9 Hz, 1H)	4.45 (dd, J = 12.0, 1.9 Hz, 1H)
	4.34 (dd, J = 12.0, 5.4 Hz, 1H)	4.30 (dd, J = 12.0, 5.4 Hz, 1H)
N—H	8.35 (d, J = 9.0 Hz, 1H)	8.34 (d, J = 9.0 Hz, 1H)

(2R)-2-Benzyloxy-4-docosen-1-ol (**7**)

A DIBAL-H solution (12.0 mL, 12 mmol, 1.0 mol/L in hexane) was added at −78 ℃ to a solution of **5** (0.61 g, 3.2 mmol) in CH_2Cl_2 (10 mL), and stirred at this temperature for 1 h, then MeOH (6 mL) was slowly added to the reaction mixture. The mixture was warmed to room temperature and stirred at ambient temperature for 0.5 h, then diluted with ether, filtered and concentrated *in vacuo*. The residue was chromatographed on a silica gel column (hexane:AcOEt, 1:1) to give **6** (0.46 g, 74%).

To a solution of octadecanyltriphenylphosphoinum bromide (4.5 g, 7.5 mmol, prepared by refluxing of a solution of 1-bromooctadecane and triphenylphosphine in xylene for 5 h at 140 ℃) in THF (15 mL) cooled to 0 ℃ was added dropwise a 2.0 mol/L solution of butyllithium in hexane (2.3 mL, 4.6 mmol), and the mixture was stirred for 1 h at this temperature. A solution of **6** (0.45 g, 2.3 mmol) in THF (5 mL) was added dropwise at 0 ℃ and then warmed to room temperature. A solution of aqueous saturated NH_4Cl (3 mL) was added dropwise to this mixture, then diluted with Et_2O, extracted with Et_2O. The combined Et_2O layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography of the residue in 5:1 petroleum ether:AcOEt gave **7** (0.86 g, 86%): TLC, R_f = 0.8 (petroleum ether:AcOEt, 4:1); ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.25—7.35 (m, 5H, Ph), 5.49—5.47 (m, 2H, H_4, H_5), 4.69 (d, J = 11 Hz, 1H, PhCH), 4.54 (d, J = 11 Hz, 1H, PhCH), 3.64 (t, J = 8 Hz, 1H, H_2), 3.53—3.55 (m, 2H, H_1), 2.31—2.34 (m, 2H, H_3), 1.95—1.97 (m, 2H, H_6), 1.22—1.27 (m, 30H, H_7—H_{21}), 0.87 (t, J = 7 Hz, 3H, H_{22}); IR (film) ν: 3427, 2925, 2854, 1468, 1456, 1350, 1207, 1097, 1029, 733, 697 cm^{-1}; MS (EI) m/z (rel. int.): 430 (M^+, 1), 91 (100), 399 (9), 43 (8), 104 (8), 55 (7), 41 (7), 57 (6), 83 (5). Anal.

calcd for $C_{29}H_{50}O_2$: C 80.93, H 11.63; found C 81.09, H 11.63.

(2R)-2-Benzyloxy-4-docosenic acid (**8**)

Pyridium dichromate (PDC) (1.93 g, 6.0 mmol) was added to a solution of **7** (0.74 g, 1.7 mmol) in DMF (15 mL), and the reaction mixture was stirred at room temperature for 36 h. After being cooled to 0 ℃, the mixture was diluted with H_2O, stirred for another 0.5 h, and filtered through a pad of Celite. The filtrate was extracted with ethyl ether. The combined ether layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column (petroleum ether:AcOEt, 4:1) to give **8** (0.47 g, 62%): TLC, R_f = 0.40 (petroleum ether : AcOEt, 4 : 1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.25—7.35 (m, 5H, Ph), 5.58—5.60 (m, 1H, H_4), 5.44—5.46 (m, 1H, H_5), 4.73 (d, J = 11 Hz, 1H, PhCH), 4.58 (d, J = 11 Hz, 1H, PhCH), 4.04 (t, J = 7 Hz, 1H, H_2), 2.61 (t, J = 7 Hz, 2H, H_3), 2.01—2.03 (m, 2H, H_6), 1.24—1.30 (m, 30H, H_{7-21}), 0.91 (t, J = 7 Hz, 3H, H_{22}); IR (film) ν: 2918, 2850, 1705, 1473, 1464, 1238, 1101, 732, 695 cm^{-1}; MS (EI) *m/z* (%) (rel. int.): 444 (M^+, 8), 426 (2), 91 (100), 57 (27), 43 (25), 55 (22), 69 (17), 41 (16), 107 (16), 83 (16). Anal. calcd for $C_{29}H_{48}O_3$: C 78.38, H 10.81; found C 78.41, H 10.91.

(2R)-2-Hydroxy-docosanic acid (**3**)

A solution of **8** (0.3 g, 0.68 mmol) in cyclohexane/anhydrous ethanol mixture (10 mL, 1:2) was hydrogenated under atmospheric pressure over Pd/C (30 mg, 10%) at 40 ℃ for 24 h. The reaction mixture was filtered through a pad of Celite and concentrate *in vacuo* to afford **3** (0.21 g, 88%) as a white solid. $[\alpha]_D^{20}$ + 12.0 (*c* 0.93, pyridine); IR (film) ν: 3447, 2955, 2920, 2852, 1750, 1467, 1377, 1262, 1095, 1028, 803, 719 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.23 (t, J = 5 Hz, 1H, H_2), 1.70—1.90 (m, 2H, H_3), 1.20—1.40 (s, 36H, H_{4-21}), 0.85 (t, J = 7 Hz, 3H, H_{22}); MS (EI) *m/z* (rel. int.): 356 (M^+, 18), 338 ($M^+ - H_2O$, 4), 311 ($M^+ - CO_2 - H$, 14), 43 (100), 55 (91), 57 (90), 41 (77), 69 (74), 83 (61), 97 (58), 71 (47).

(2R)-2-Acetoxydocosanic acid (**9**)

Pyridine (0.5 mL) and acetic anhydride (0.3 mL) were added to a solution of **3** (0.07 g, 0.20 mmol) in dry CH_2Cl_2 (2.0 mL). The reaction mixture was stirred at room temperature overnight. Then it was diluted with $CHCl_3$, washed with water, and saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give **9** (0.076 g, 97%) as a white solid: TLC, R_f = 0.2 (petroleum ether:AcOEt, 4:1); $[\alpha]_D^{20}$ + 6.6 (*c* 0.5, $CHCl_3$), lit.[11] $[\alpha]_D^{20}$ + 4.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 60 MHz,) δ: 5.30 (s-like, 1H, H_2), 2.15 (s, 3H, $COCH_3$), 1.60 (s, 2H, H_3), 1.20 (s-like, 36H, H_{4-21}), 0.90 (s-like, 3H, H_{22}).

Succinimidoxy (2R)-2-acetoxy-docosanate (**10**)

To a solution of **9** (0.044 g, 0.11 mmol) in CH_2Cl_2 (2 mL) was added *N*-hydroxy succinimide (14 mg, 0.12 mmol) and dicyclohexylcarbodiimide (DCC) (26.2 mg). Then the mixture was stirred for 7 h. The resulted precipitate was filtered off. The filtrate was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was chromatographed on a silica gel column (petroleum ether : AcOEt, 5:1) to give **10** (41 mg, 80%): TLC, R_f = 0.30 (petroleum ether : AcOEt, 5 : 1); ^{1}H NMR ($CDCl_3$, 90 MHz) δ: 5.30 (s, 1H, H_2), 2.80 (s, 4H), 2.15 (s, 3H, $COCH_3$), 1.60 (s, 2H, H_3), 1.20 (s-like, 36H, H_{4-21}), 0.90 (s-like, 3H, H_{22}); MS (EI) *m/z* (rel. int.): 496 (M^+ + H, 1), 43 (100), 41 (18), 353 (17), 381 (12), 55 (11), 57 (10), 97 (9), 96 (7).

(2S,3R,4E,8E)-2-[(R)-2-Acetoxydocosanoylamino]-4,8-octadecadiene-1,3-diol (**11**)

Et_3N (12 μL) and DMAP (2 mg) were added to a solution of **2** (17.5 mg, 59 μmol) and **10** (35 mg, 70.7 μmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was chromatographed on a silica gel column (petroleum ether:AcOEt, 2:1) to give **11** (38 mg, 95%): TLC, R_f = 0.25 (petroleum ether:AcOEt, 2:1); $[\alpha]_D^{20}$ + 10.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.80 (*d*, J = 8 Hz, 1H, NH), 5.80 (dt, J = 16, 6 Hz, 1H, H_5), 5.53 (dd, J = 16, 6 Hz, 1H, H_4), 5.41—5.44 (m, 2H, $H_{8,9}$), 5.09 (t, J = 7 Hz, 1H, $H_{2'}$), 4.35 (s-like, 1H, H_2), 3.97 (dd, J = 11, 3 Hz, 1H, H_{1a}), 3.87 (dd, J = 7, 3 Hz, 1H, H_3), 3.69 (dd, J = 11, 3 Hz, H_{1b}), 2.16 (s, 3H, $COCH_3$), 1.80—2.10 (m, 10H, $H_{6,7,10,3',4'}$), 1.26 (s-like, 50H, $H_{11-17,4'-21'}$), 0.88 (t, J = 7 Hz, 6H, $H_{18,22'}$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 61.9 (C_1), 54.1 (C_2), 74.2 (C_3), 133.6, 131.4 (C_4, C_5), 31.94*, 31.93* (C_6, C_7), 128.9, 128.9 (C8,9), 31.89* (C_{10}), 29.2—29.7 (C_{11-15}), 32.1 (C_{16}), 22.7 (C_{17}), 14.1 (C_{18}), 170.6 ($C_{1'}$), 74.5 ($C_{2'}$), 32.6 ($C_{3'}$), 24.9 ($C_{4'}$), 29.2—29.7 ($C_{5'-19'}$), 32.4 ($C_{20'}$), 22.7 ($C_{21'}$), 14.1 ($C_{22'}$), 170.2 ($COCH_3$), 21.0 ($COCH_3$) (* indicating that these data are interchangeable); IR (film) ν: 3337, 2957, 2923, 1754, 1659, 1627, 1544, 1467, 1379, 1223, 1034, 962, 803, 724, 682, 605 cm^{-1}; MS (ESI) *m/z*: 678.6 (M^+ + H), 660.7 (M^+ + H − H_2O); MS (EI) *m/z* (rel. int.): 660 (M^+ + H − H_2O), 43 (100), 380 (35), 60 (33), 422 (30), 41 (33), 55 (30), 350 (29), 57 (28); HRSIMS *m/z*: 678.6051 [M + H]$^+$ (calcd 678.6031 for $C_{42}H_{80}O_5N$).

(2S,3R,4E,8E)-2-[(R)-2-Hydroxydocosanoylamino]-4,8-octadecadiene-1,3-diol (**12**)

A 0.1 mol/L solution of K_2CO_3 in MeOH (0.8 mL) was added to a solution of **11** (32 mg, 47 μmol) in MeOH (1 mL). After being stirred at room temperature for 1h, the reaction mixture was concentrate *in vacuo* and the residue was chromatographed on a silica gel column (petroleum ether : AcOEt, 1:1) to give **12** (27 mg, 90%): TLC, R_f = 0.45 (petroleum ether:AcOEt, 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.20 (d, J = 6 Hz, 1H, NH), 5.77—5.80 (m, 1H, H_5), 5.56—5.58 (m, 1H, H_4), 5.40—5.44 (m, 2H, $H_{8,9}$), 4.32—4.34 (m, 1H, H_3), 4.16—4.18 (m, 1H, $H_{2'}$), 3.96—3.98 (m, 2H, H_1), 3.77—3.79 (m, 1H, H_2), 1.80—2.10 (m, 10H, $H_{6,7,10,3',4'}$), 1.26 (s-like, 50H, $H_{11-17,\ 4'-21'}$), 0.88 (t, J = 7 Hz, 6H, $H_{18,22'}$).

(2S,3R,4E,8E)-2-[(R)-2-Benzoyloxy docosanoylamino]-3-O-benzoyl-4,8-octadecadiene-1,3-diol (**13**)

A solution of **12** (23 mg, 34 μmol), trityl chloride (14 mg, 51 μmol), and 4-(dimethyl amino)-pyridine (DMAP) (1 mg, 8.8 μmol) in pyridine (0.5 mL) was stirred at 80 ℃ for 7 h, and cooled to room temperature. Benzoyl chloride (10 μL, 8 μmol) was added dropwise, and the reaction mixture was then stirred at room temperature for 7 h. After the addition of MeOH (20 μL), the mixture was stirred at room temperature for 1 h, diluted with $CHCl_3$, and washed with water. The $CHCl_3$ layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a yellow residue, which was used for the next reaction without purification. The residue was dissolved in a solution of TsOH monohydrate (20 mg, 100 μL) in $CHCl_3$ and MeOH (1.5 mL, 1:1). The reaction mixture was stirred at room temperature for 8 h, poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extracts was washed with brine, then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was chromatographed on a silica gel column (petroleum ether:AcOEt, 8:1) to afford **13** (23 mg, 77%) as a white solid: TLC, R_f = 0.25 (petroleum ether:AcOEt, 5.5:1); $[\alpha]_D^{20}$ + 6.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz,) δ: 7.95—8.25 (m, 4H, Ph), 7.45—7.75 (m, 2H, Ph), 7.50—7.54 (m, 2H, Ph), 6.89 (d, J = 8 Hz, 1H, NH), 5.86—5.88 (m, 1H, H_5), 5.62—5.68 (m, 2H, $H_{8,9}$), 5.42—5.46 (m, 1H, H_4), 5.33—5.35 (m, 2H, $H_{2',3}$), 4.30 (s, 1H, H_2), 3.72—3.74 (m, 2H, H_1), 1.80—2.10 (m, 10H, $H_{6,7,10,3',4'}$), 1.26 (s-like, 50H, $H_{11-17,\ 4'-21'}$), 0.88 (t, J = 6 Hz, 6H, $H_{18,22'}$); IR (film) ν: 3501—3188, 2920, 2851, 1735, 1698, 1659, 1618, 1548, 1263, 1111, 1071, 965, 836, 752, 708, 620 cm^{-1}; MS (ESI) *m/z*: 866.8 ($M + Na^+$), 722.7 ($M^+ - PhCOO$).

1-O-(2,3,4,6-Tetra-O-benzoyl-β-D-glucopyranosyloxy)-(2S,3R,4E,8E)-2-[2(R)-benzoyloxydocosanoylamino]-3-benzoyloxy-4,8-octadecadiene (**15**)

A solution of 2,3,4,6-tetra-*O*-benzoyl-α-*D*-glucopyranosyl trichloroacetimidate (**14**) (37 mg, 49.6 μmol, prepared by the reported method[12]), **13** (22 mg, 26 μmol) and oven-dried powdered 4 Å molecular sieves (30 mg) in CH_2Cl_2 (1.5 mL) was stirred under nitrogen at room temperature for 30 min before being cooled to − 20 ℃. To this suspension, was added TMSOTf (2 μL), and the mixture was stirred at − 20—0 ℃ for 2 h. The solution was then neutralized with Et_3N and concentrated to dryness. Flash chromatography of the residue on a silica gel column (petroleum ether:AcOEt, 5.5:1) to give **15** (25 mg, 68%) as a viscous, colorless liquid: TLC, R_f = 0.30 (petroleum ether:AcOEt, 5.5:1); UV λ_{max}: 231 nm; HPLC was used to identify the purity of **15**, HPLC: LKB 2150 PUMP; detector: UV 231 nm, rate of the paper: 5 mm/min; mobile phase: MeOH; flow rate: 1 mL/min; retention time: 22 min (single peak); $[\alpha]_D^{20}$ + 20.8 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.88—8.05 (m, 10H, Ph), 7.26—7.48 (m, 20H, Ph), 6.60 (d, J = 9 Hz, 1H, NH), 6.31 (d, J = 8 Hz, 1H), 6.04 (t, J = 10 Hz, 1H), 5.83 (dd, J = 9, 10 Hz, 2H), 5.24—5.71 (m, 4H, $H_{3,4,8,9}$), 4.80 (d, J = 8 Hz, 1H), 4.62—4.66 (m, 2H), 4.50 (dd, J = 5, 12 Hz, 2H), 4.80 (d, J = 8 Hz, 1H,), 4.62—4.65 (m, 2H), 4.50 (dd, J = 5, 12 Hz, 2H), 4.41 (m, 2H), 4.07 (dd, J = 5, 12 Hz, 1H), 3.75 (dd, J = 5, 12 Hz 1H), 1.80—2.10 (m, 10H, $H_{6,7,10,3',4'}$), 1.26 (s-like, 50H, $H_{11-17,\ 4'-21'}$), 0.88 (t, J = 7 Hz, 6H, $H_{18,22'}$); IR (film) ν 2926—2854, 1732, 1602, 1585, 1452, 1316, 1267, 1178, 1070, 757, 709 cm^{-1}; MS (ESI) *m/z*: (rel. int.) 1423.8 ($M + H^+$, 8), 723.5 (28).

1-O-β-D-Glucopyranosyl-(2S,3R,4E,8E)-2-[2(R)-hydroxy-docosanoylamino]-4,8-octadecadiene-1,3-diol (**1**)

A 0.1 mol/L solution of NaOMe in MeOH (1.2 mL) was added to a solution of **15** (25 mg) in MeOH and THF (2 mL, 1:1). After being stirred at room temperature for 1 h, the reaction mixture was concentrated by blowing a stream of nitrogen gas over it, and the residue was chromatographed on asilica gel column (CH_2Cl_2:MeOH, 4:1) to give **1** (10 mg, 72%) as a white solid: TLC, R_f = 0.40 (CH_2Cl_2:MeOH, 4:1); $[\alpha]_D^{20}$ + 4.0 (*c* 0.28, $CHCl_3$:MeOH, 1:1); ^{1}H NMR (C_5D_5N, 500 MHz) see Table 1. MS (ESI) *m/z*: 820.7 [M + Na]$^+$, 803.6 [M + Na − H_2O]$^+$; EIMS *m/z* (rel. int.): 780 (5), 617 (12), 599 (5), 586 (12), 450 (5), 432 (9), 398 (7), 381 (73), 356 (32), 337 (3), 311 (5), 288 (5), 280 (7), 262 (26), 248 (28), 222 (17), 145 (13), 97 (46), 69 (100).

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