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Syntheses and Cytotoxicities of Four Stereoisomers of Muricatacin from D-Glucose

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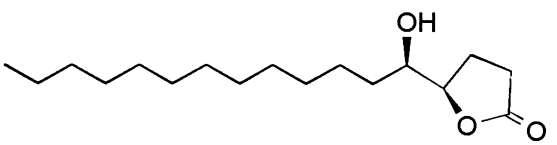
Abstract—Four stereoisomers of muricatacin **1a–d** were prepared by the reaction of corresponding aldehydes **4a–d**, which in turn were prepared from D-glucose, with the anion of triethylphosphonoacetate followed by reduction and cyclization under acidic conditions. Cytotoxicities of four stereoisomers were tested against in vitro A-549 cell line as well as MCF-7 cell line. Stereochemistry at C_4 and C_5 position of muricatacin did not affect the cytotoxicities significantly.

Introduction

Muricatacin (**1**), an acetogenin derivative, which is isolated from the seeds of the tropical fruit *Annona muricata* L., has received a great deal of attention because it shows some cytotoxicities against human tumor cell lines and its congeners show a wide range of biological activities.[1] The natural muricatacin is comprised of (−)-(4*R*,5*R*)-5-hydroxyheptadeca-4-nolide and its (+)-(4*S*,5*S*) enantiomer, with the former predominating. (+)-Muricatacin and/or (−)-muricatacin was recently synthesized from various starting materials.[2]



(–)–(4*R*,5*R*)–Muricatacin

In connection with our projects to explore the structure-activity relationship of acetogenin derivatives, we needed to prepare four stereoisomers of muricatacin to understand the effect of stereochemistry at C_4 and C_5 position of muricatacin on cytotoxicity. Here, we report a stereocontrolled synthesis of four enantiomerically pure stereoisomers of muricatacin, (−)-(4*R*,5*R*), (+)-(4*S*,5*R*), (−)-(4*R*,5*S*), and (+)-(4*S*,5*S*)-enantiomers from D-glucose, as well as their cytotoxicities.

Results and Discussion

Synthesis

According to Scheme 1, the synthesis of (−)-(4*R*,5*R*)-muricatacin (**1a**) started from 5,6-dideoxy-1,2-isopropylidene-5-C-(*n*-undecanyl)-α-D-glucofuranose (**2**) which was available from D-glucose in four steps.[3–6] Monoprotection of **2** with benzyl chloride in tetrahydrofuran (THF) using NaH as a base, followed by removal of the isopropylidene group with 9.6 N HCl, afforded 1,2-diol compound **3**. Oxidative cleavage of **3** with sodium periodate gave (2*S*,3*R*)-*O*-protected 2,3-dihydroxy aldehyde **4a**. Horner–Emmons olefination of the aldehyde **4a** with the anion of triethylphosphonoacetate gave (*E*)-unsaturated ester **5a** in 73% yield. Hydrogenation of **5a** in the presence of 10% Pd-C under 1 atm of hydrogen followed by treatment of

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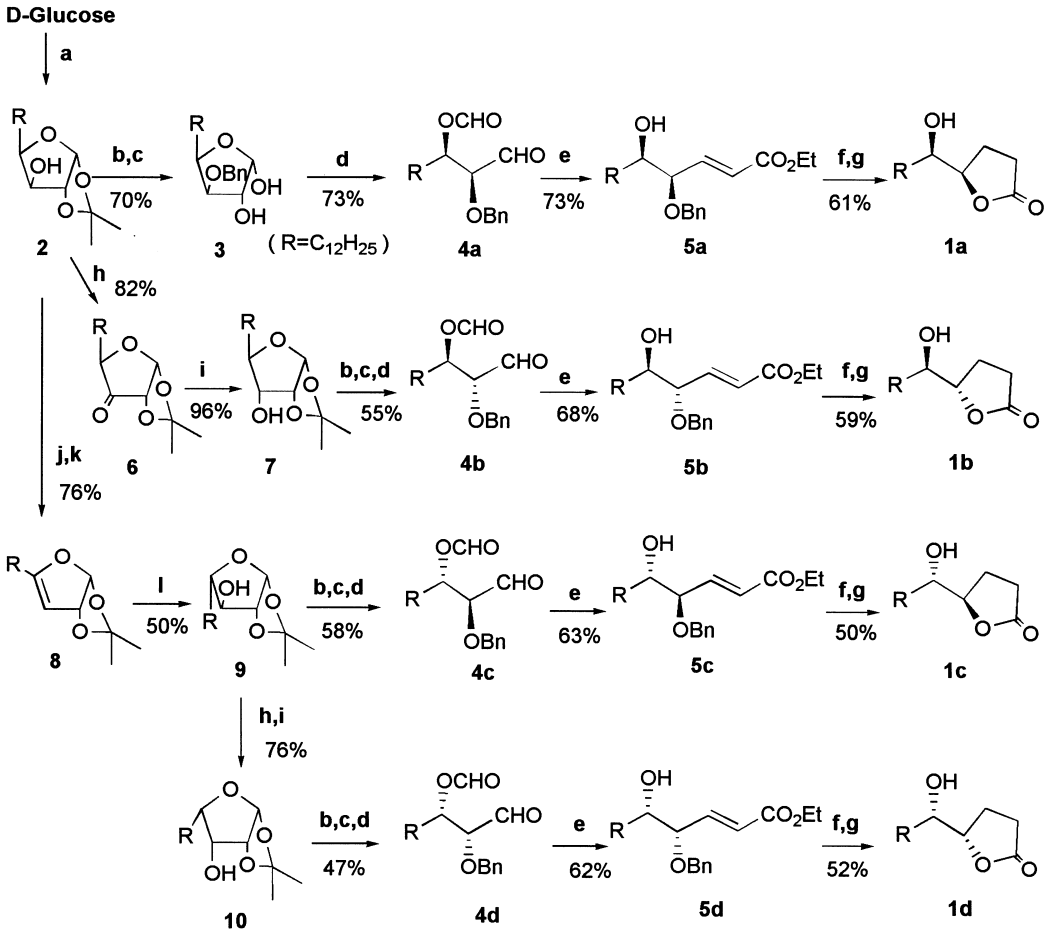

Scheme 1. Preparation of muricatacin **1a–d**. (a) See reference[7]; (b) NaH, BnCl, THF, rt, 5h; (c) 9,6 N HCl/TFA, DME, rt, 48h; (d) $NaIO_4$, MeOH, rt, 1h; (e) NaH, $(EtO)_2POCH_2CO_2Et$, THF, rt 3h; (f) H_2, Pd-C, EtOAc, rt, 24h; (g) TFA-H_2O (4:1), rt, 3h; (h) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −60 °C→rt, 2h; (i) $NaBH_4$, MeOH, rt; (j) Tf_2O, pyridine, CH_2Cl_2, −10 °C; (k) DBU, ether, rt; (l) Sia_2BH, THF, 0 °C→rt, then H_2O_2, aq. NaOH.

trifluoroacetic acid afforded (−)-(4*R*,5*R*)-muricatacin (**1a**) in 45% overall yield from **4a**.[7] Therefore, in order to synthesize the remained three stereoisomers of (−)-(4*R*,S*R*)-murcatacin, we first needed to prepare the appropriately stereocontrolled *0*-protected 2,3-dihydroxy aldehydes **4b-4d**.

The corresponding (2*R*,3*R*)-*O*-protected 2,3-dihydroxy aldehyde **4b** required for the synthesis of (4*S*,5*R*)-muricatacin **1b** was prepared from the C-3 unprotected furanose **2**. In order to introduce *S* configuration at C_3 position, the C_3 β-hydroxyl group in **2** was oxidized to the ketone **6** under Swern oxidation condition,[8] and **6** was subsequently reduced with $NaBH_4$ in MeOH at room temperature[9] to afford the C_3 α-hydroxyl compound **7** as the sole isolated product. After protection of the hydroxy group in **7** with benzyl group, the isopropylidene group was removed with 9.6 N HCl/TFA to provide the hemiacetal, which was subjected to the oxidative cleavage with sodium periodate to give the (2*R*,3*R*)-2-benzyloxy-3-formyloxy-1-pentadecanal **4b**.

The synthesis of (2*S*,3*S*)-*O*-protected 2,3-dihydroxy aldehyde **4c** was first undertaken by changing the C_4 β-oriented dodecyl group in **2** into α-oriented one. For this purpose, dodeca-3-enofuranose **8** was prepared by the elimination reaction of the triflate derived from the *O*-triflation of the C_3 hydroxyfuranose **2** with trifluoromethanesulfonic anhydride in pyridine.[10] Hydroboration[11] of **8** with disiamylborane followed by oxidation with H_2O_2/NaOH afforded the 3-hydroxyl-β-L-xylofuranose **9** exclusively with 60% yield after separation by silica gel column (230–400 mesh) chromatography. After preparation of **9**, the same reaction conditions for the synthesis of **4a** from **2** were used to convert **9** into **4c**.

Table 1. In vitro inhibition of A-549 and MCF-7 cell lines

Compd	IC_{50} (μg/mL)	
	A-549	MCF-7
1a	18.5	17.6
1b	29.8	16.7
1c	23.7	22.2
1d	24.3	15.9

Similar approaches were used to prepare the (2*R*,3*S*)-*O*-protected 2,3-dihydroxy aldehyde **4d**. Thus, after the C_3 α-oriented compound **10** was prepared from **9** possessing the C_3 β-hydroxyl group by the use of the methods applied in the synthesis of **7** from **2**, it was subsequently converted into **4d** by the same reaction sequences described for the synthesis of **4b** from **7**. Finally, the three remaining (+)-(4*S*,5*R*), (−)-(4*R*,5*S*) and (+)-(4*S*,5*S*)-enantiomers **1b–d** were synthesized from **4b**, **4c**, and **4d**, respectively, by the methods for the synthesis of (−)-(4*R*,5*R*) muricatacin (**1a**) from **4a**.

Cytotoxicities

The cytotoxicities of **1a–d** were tested against in vitro A-549 cell line as well as MCF-7 cell line by measuring the inhibition of cell growth.[12] As shown in Table 1, the four stereoisomers generally exhibited weak and similar inhibition in both cell lines. Although (4*R*,5*R*)-compound **1a** showed a slightly higher cell growth inhibition in A-549 cell line compared to the rest of the stereoisomers, the difference was minimal. This indicates that the stereochemistry at C_4 and C_5 position of muricatacin might not affect the cytotoxicities significantly.

Conclusion

In conclusion, we have established efficient methods for the syntheses of four stereoisomers **1a-1d** of muricatacin (**1**) from D-glucose and found that the stereochemistry at C_4 and C_5 position of muricatacin did not affect the cytotoxicities significantly.

Experimental

Chemistry

Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. Optical rotations were determined at a sodium D line using a JasCo 370-DIP polarimeter and measured in chloroform. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer at 200 MHz and 50 MHz. Chemical shifts were given in relative tetramethylsilane. Infrared spectra were recorded on a Nicolet FT-IR 550 spectrometer. GC-Mass spectroscopy was carried out on a Hewlett Packard (5972 series) instrument. Elemental analyses were performed by Fisons Eager 200 instrument, Italy. Flash column chromatography was done by using Merck silica gel 60 (15–40 μm). Following abbreviations are used for reagent and solvents: DBU (1,8-diazabicyclo[5,4,0] undec-7-ene), DME (1,2-dimethoxyethane), DMSO (dimethyl sulfoxide), THF (tetrahydrofuran).

5,6-Dideoxy-1,2-isopropylidene-5-*C*-(*n*-undecanyl)-α-D-glucofuranose (2). This was prepared from D-glucose according to the procedure reported by S-K Kang et al.[7] White solid; mp 76–77 °C; $[\alpha]^{20}_D = -24.8°$ (c = 10.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, J = 6.7 Hz, $-CH_3$), 1.02–1.45 (m, 22H, $-(CH_2)_{11}-$), 1.32 (s, 3H acetonide), 1.63 (s, 3H, acetonide), 2.02 (d, 1H J = 6.2 Hz, OH), 4.01–4.12 (m, 2H, C_3-H and C_4-H), 4.52 (d, 1H, J = 3.8 Hz, C_2-H), 5.86 (d, 1H, J = 3.8 Hz, C_1-H); ^{13}C NMR ($CDCl_3$) δ 4.1, 22.7, 26.1, 26.6, 29.3, 30.7, 31.9, 75.4 (C_4), 80.3 (C_2), 85.3 (C_3), 104.2 (C_1), 111.4 (C_7).

3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-dihydroxy-5-*C*-(*n*-undecanyl)-α-D-glucofuranose (3). To a suspension of NaH (610 mg of 95% powder, 25.4 mmol) in anhydrous DMSO (30 mL) was added **2** (5.1 g, 19.6 mmol) in anhydrous THF (150 mL) under a nitrogen atmosphere. After the mixture was stirred for 30 min at room temperature, benzyl chloride (3.2 g, 25.4 mmol) was added. The reaction mixture was stirred for 5 h at room temperature and then quenched with saturated aqueous NH_4Cl solution (50 mL). The organic solvent was removed and the aqueous solution was extracted with CH_2Cl_2 (50 mL × 3). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The crude product was chromatographed on a silica gel column (hexane:ethyl acetate = 1:1) to give a 3-*O*-benzyl-1,2,5,6-diisopropylidene-α-D-glucofuranose (7.3 g, 96%) as slightly yellow oil: IR (neat) 3060, 3040, 2980, 2890 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.6 Hz, $-CH_3$), 1.12–1.48 (m 22H, $-(CH_2)_{11}-$), 1.31 (s, 3H, acetonide), 1.63 (s, 3H, acetonide), 3.75 (d, 1H, J = 3.0 Hz, C_3-H), 4.05–4.18 (m, 1H, C_4-H), 4.43–4.72 (m, 3H, $-OCH_2$ and C_2-H), 5.90 (d, 1H, J = 3.9 Hz, C_1-H), 7.32 (m, 5H, phenyl). To a solution of 3-*O*-benzylated compound (6.3 g, 15.1 mmol) in DME (20 mL) was slowly added dropwise 9.6N HCl (10 mL). The reaction mixture was stirred for 48 h at room temperature and then neutralized with saturated aqueous $NaHCO_3$ solution. After the evaporation of DME, the aqueous layer was extracted with CH_2Cl_2 (30 mL × 3). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a silica gel column (hexane:ethyl acetate = 1:2) to give **3** (3.8 g, 67%) as a white solid mp 52–53 °C; IR (neat)

3550, 2990, 2850, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 6.6 Hz, $-CH_3$), 1.14–1.58 (m, 22H, $-(CH_2)_{11}$-), 1.63 (m, 1H, –OH), 3.8 (m, 1H, C_3-H), 4.23 (m, 2H, C_2-H & C_4-H) 4.53–4.75 (dd, 2H, J = 11.9, 49.9 Hz, $-OCH_2$), 5.45 (d, 1H, J = 4.1 Hz, C_1-H), 7.32 (s, 5H, -phenyl).

(2*S*,3*R*)-2-Benzyloxy-3-formyloxy-1-pentadecanal (4a). To a solution of **3** (3.7 g, 9.8 mmol) in MeOH (200 mL) was added 0.6N $NaIO_4$ solution (250 mL). The reaction mixture was stirred for 1 h at room temperature and then concentrated. After the reaction mixture was diluted with H_2O (50 mL), it was extracted with CH_2Cl_2 (30 mL×3). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a silica gel column (hexane:ethyl acetate = 1:2) to give **4a** (2.7 g, 73%) as a white solid: mp 30–31 °C, $[\alpha]^{20}_D$ = 11.62° (c = 11.7, $CHCl_3$); IR (neat) 3050, 2935, 2850, 1737, 1713, 1173 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 6.6 Hz, –CH_3), 1.32 (s, 20H, –$(CH_2)_{10}$–), 1.69 (m, 2H, –CH_2), 3.88 (dd, 1H, J = 0.9, 3.1 Hz, C_2-H), 4.55–4.86 (dd, 2H, J = 11.9, 49.7 Hz, –OCH_2), 5.28 (m, 1H, C_3-H), 7.34 (s, 5H,-phenyl), 8.05 (s, 1H, –OCHO), 9.66 (d, 1H, J = 1.0 Hz, –CHO); ^{13}C NMR ($CDCl_3$) δ 15.5, 24.0, 26.5, 30.5, 31.3, 33.3, 73.8 (C_3), 74.8 (–OCH_2), 84.1 (C_2), 129.4, 129.5, 129.9, 137.9, 161.6 (–OCHO), 202.4 (–CHO).

Ethyl (4*R*,5*R*)-4-benzyloxy-5-hydroxy-(2*E*)-heptadecanoate (5a). To a suspension of NaH (250 mg of 95% powder, 10.4 mmol) in anhydrous THF (10 mL) was slowly added a solution of triethyl phosphonoacetate (1.9 g, 8.5 mmol) in anhydrous THF (5 mL). The reaction mixture was stirred for 30 min at 0 °C, and compound **4a** (2.5 g, 6.6 mmol) in THF (10 mL) was slowly added to this mixture. The reaction mixture was stirred for 3 h at room temperature under a nitrogen atmosphere and then quenched with NH_4Cl solution (30 mL). After the organic solvent was removed, the aqueous layer was extracted with CH_2Cl_2 (50 mL×3). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a silica gel column (hexane:ethyl acetate = 1:1) to give **5a** (2.0 g, 73%) as a slightly yellow oil: IR (neat) 3480 (–OH), 3040, 2930, 2860, 1730 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3H, J = 6.8 Hz, –CH_3), 1.25–1.58 (m, 25H, –$(CH_2)_{11}$– and –CH_3), 2.62 (d, 1H, J = 3.1 Hz, –OH), 3.68 (m, 1H, C_5-H), 3.83 (m, 1H, C_4-H), 4.23 (q, 2H, J = 4.6 Hz, –CO_2CH_2–), 4.32–4.69 (dd, 2H, J = 11.8, 50.1 Hz, –OCH_2), 6.13 (d, 1H, J = 14.6 Hz, C_2-H), 6.87 (dd, 1H, J = 14.6, 6.7 Hz, C_3-H), 7.33 (s, 5H, –phenyl); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 25.5, 29.3, 29.5, 31.8, 32.6, 51.7, 71.4 (C_5), 73.3 (–OCH_2), 81.9 (C_4), 124.0 (C_2), 127.9, 128.0, 128.5, 137.4, 144.8 (C_3), 166.3.

(−)-(4*R*,5*R*)-5-Hydroxyheptadeca-4-nolide (1a). In the presence of 10% Pd-C (500 mg), a solution of **5a** (1.2 g, 2.9 mmol) in ethyl acetate (100 mL) was hydrogenated under an atmosphere of hydrogen for 24 h at room temperature. The catalyst was filtered and the filtrate was concentrated to give the corresponding saturated ester as a white solid. The ester was dissolved in H_2O-trifluoroacetic acid (4:1) (100 mL) and the resulting solution was stirred for 3 h at room temperature. After the solution was neutralized with saturated aqueous $NaHCO_3$ solution, the neutralized aqueous layer was extracted with chloroform (30 mL×3). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a silica gel column (hexane:ethyl acetate = 1:2) to give the product, which was recrystallized from hexane-ethyl acetate (10:1) to give **1a** (500 mg, 61%) as a white solid: mp 71–72 °C, lit.[2c] 73–74 °C, lit.[1] 50 °C, lit.[2f] 72 °C, $[\alpha]^{20}_D$ = −11.62° (c = 11.7, $CHCl_3$), lit.[2c] −23.14° (c = 2.36, $CHCl_3$), lit.[2a] −22.9° (c = 1.1, $CHCl_3$); IR (KBr) 3400 (-OH), 2960, 2920, 1753 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3H, J = 6.8 Hz, –CH_3), 1.25–1.56 (s, 22H, –$(CH_2)_{11}$–), 2.08 (s, 1H, –OH), 2.12–2.48 (m, 2H, C_3-H), 2.61 (m, 2H, C_2-H), 3.56 (m, 1H, C_5-H), 4.43 (ddd, 1H, J = 3.2, 7.3, 10.6 Hz, C_4-H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.5, 23.9, 25.3, 28.5, 29.2, 29.3, 31.7, 73.5 (C_5), 82.78 (C_4), 177.05 (C_1); Mass (m/e) 285 (MH^+), 267, 199, 180, 97, 86 (base peak); Anal. calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.84; H, 11.48.

5,6-Dideoxy-1,2-isopropylidene-3-carbonyl-5-*C*-(*n*-undecanyl)-α-D-allofuranose (6). A solution of oxaloyl chloride (0.26 mL, 3.1 mmol) and DMSO (3 mL) in CH_2Cl_2 (25 mL) was stirred for 15 min at −60 °C under a nitrogen atmosphere. To this solution was added **2** (640 mg, 2.0 mmol) in CH_2Cl_2 (15 mL). After the reaction mixture was stirred for 50 min at −60 °C, Et_3N (5 mL) was added and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with H_2O (20 mL) and then extracted with CH_2Cl_2 (30 mL×3). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a silica gel column (hexane:ethyl acetate = 1:1) to give **6** (530 mg, 82%) as a white solid: mp 66–67 °C; IR (KBr) 2960, 2890, 1820 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 6.6 Hz, –CH_3), 1.02–1.45 (s, 22H, $(CH_2)_{11}$–), 1.38 (s, 3H, acetonide), 1.50 (s, 3H, acetonide), 4.32 (m, 2H, C_2-H and C_4-H), 5.86 (d, 1H, J = 4.1 Hz, C_1-H).

5,6-Dideoxy-1,2-isopropylidene-5-*C*-(*n*-undecanyl)-α-D-allofuranose (7). To a solution of **6** (430 mg, 1.3 mmol) in MeOH (150 mL) was added $NaBH_4$ (250 mg, 6.7 mmol) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. After the evaporation of methanol, the reaction mixture was diluted with water (50 mL) and then extracted with CH_2Cl_2 (30 mL×3). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a silica gel column (hexane:ethyl acetate = 1:1) to give **7**

(410 mg, 96%) as a white solid: mp 81–82 °C, $[\alpha]^{20}_D = +46.4°$ (c = 10.0, $CHCl_3$); IR (KBr) 3480 (–OH), 2960, 2880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3H, $J = 6.9$ Hz, $–CH_3$), 1.21–1.52 (m, 22H, $–(CH_2)_{11}–$), 1.31 (s, 3H, acetonide), 1.62 (s, 3H, acetonide), 2.32 (d, 1H, $J = 7.9$ Hz, –OH), 3.52–3.82 (m, 2H, C_3-H and C_4-H), 4.5 (t, 1H, $J = 4.1$ Hz, C_2-H), 5.79 (d, 1H, $J = 4.0$ Hz, C_1-H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.7, 29.3, 29.7, 31.9, 75.4 (C_4), 80.3 (C_2), 85.3 (C_3), 104.2 (C_1), 111.4 (C_7).

(2*R*,3*R*)-2-Benzyloxy-3-formyloxy-1-pentadecanal (4b). 7 (400 mg, 1.2 mmol) was subjected to the same sequence of the reactions as described for the synthesis of **4a** from **2**. Benzylation of **7** (480 mg, 96%), followed by the cleavage of the isopropylidene group, gave the 1,2-diol compound (280 mg, 65%): IR (neat) 3500, 2950, 2850, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, $J = 6.6$ Hz, $–CH_3$), 1.13–1.58 (m, 22H, $–(CH_2)_{11}–$), 1.72 (m, 1H, –OH), 3.56 (m, 1H, C_3-H), 3.95–4.20 (m, 2H, C_2-H and C_4-H), 4.65 (s, 2H, $–OCH_2$), 5.25 (m, 1H, C_1-H), 7.34 (s, 5H, -phenyl). Oxidative cleavage reaction of the 1,2-*O*-diol compound gave **4b** (250 mg, 55%) as a slightly yellow oil: $[\alpha]^{20}_D = +29.9°$ (c = 11.9, $CHCl_3$); IR (neat) 3050, 2960, 2850, 1760, 1480 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, $J = 6.9$ Hz, $–CH_3$), 1.32 (s, 20H, $–(CH_2)_{10}–$), 1.65 (m, 2H, $–CH_2$), 3.87 (dd, 1H, $J = 1.9$, 3.4 Hz, C_2-H), 4.68 (s, 2H, $–OCH_2$), 5.38 (m, 1H, C_3-H), 7.33 (s, 5H, –phenyl), 8.07 (s, 1H, –OCHO), 9.65 (d, 1H, $J = 2.0$ Hz, –CHO); ^{13}C NMR ($CDCl_3$) δ 15.4, 24,0, 26.6, 30.7, 31.0, 33.2 (C_3), 74.3 ($–OCH_2$), 84.9 (C_2), 129.3, 129.5, 129.9, 138.0, 161.6 (–OCHO), 202.3 (–CHO).

Ethyl (4*S*,5*R*)-4-benzyloxy-5-hydroxy-(2*E*)-heptadecanoate (5b). 4b (250 mg, 0.66 mmol) was subjected to the same reaction described for the synthesis of **5a**. **5b** (186 mg, 68%) was obtained as a slightly yellow oil: IR (neat) 3420 (–OH), 3050, 2920, 2860, 1730 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3H, $J = 6.8$ Hz, $–CH_3$), 1.21–1.52 (m, 25H, $–(CH_2)_{11}–$ and $–CH_3$), 2.28 (m, 1H, –OH), 3.88 (m, 1H, C_5-H), 3.95 (m, 1H, C_4-H), 4.21 (q, 2H, $J = 4.5$ Hz, $–CO_2CH_2–$), 4.37–4.72 (dd, 2H, $J = 11.5$, 49.7 Hz, $–OCH_2$), 6.11 (d, 1H, $J = 14.5$ Hz, C_2-H), 6.96 (dd, 1H, $J = 14.5$, 6.8 Hz, C_3-H), 7.35 (s, 5H, -phenyl); ^{13}C NMR ($CDCl_3$) δ 15.5, 24.0, 27.1, 30.7, 30.9, 33.5, 55.0, 72.6 (C_5), 74.5 ($–OCH_2$), 82.7 (C_4), 126.0 (C_2), 129.0, 129.1, 129.8, 138.9, 145.3 (C_3), 167.1.

(+)-(4*S*,5*R*)-5-Hydroxyheptadeca-4-nolide (1b). 5b (120 mg, 0.29 mmol) was subjected to the same reaction described for the synthesis of **1a**. **1b** (48 mg, 59%) was obtained as a white solid: mp 71.5 °C; $[\alpha]^{20}_D = +14.3°$ (c = 7.4, $CHCl_3$); IR (KBr) 3430 (–OH), 2960, 2920, 1780 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3H, $J = 6.8$ Hz, $–CH_3$), 1.23–1.55 (s, 22H, $–(CH_2)_{11}–$), 1.92 (s, 1H, –OH), 2.12–2.47 (m, 2H, C_3-H), 2.59 (m, 2H, C_2-H), 3.95 (m, 1H, C_5-H), 4.55 (ddd, 1H, $J = 3.2$, 7.3, 10.6 Hz, C_4-H); ^{13}C NMR ($CDCl_3$) δ 13.9, 21.8, 23.1, 25.9, 28.5, 29.2, 29.5, 31.9, 71.9 (C_5), 82.5 (C_4), 177.1 (C_1); Mass (m/e) 285 (MH^+), 266, 199, 111, 86 (base peak); Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.53; H, 11.58.

3,5,6-Trideoxy-1,2-*O*-isopropylidene-α-D-erythro-dode-3-cenofuranose (8). To a solution of **2** (3.5 g, 7.0 mmol) in CH_2Cl_2 (100 mL) was added pyridine (2 mL). After the solution was stirred for 30 min at −10 °C, trifluoromethanesulfonic anhydride (3.9 g, 13.9 mmol) was carefully added. The reaction mixture was stirred for 1 h at −10 °C under a nitrogen atmosphere and then diluted with ether (100 mL) to give a white precipitate. After filtration of the precipitate, the filtrate was successively washed with H_2O, 5% HCl, saturated aqueous $NaHCO_3$ solution, and saturated aqueous NH_4Cl solution. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a silica gel column (hexane:ethyl acetate = 1:2) to give the triflated compound (5.1 g, 94%) as a slightly yellow oil. To a solution of the triflated compound (5.1 g, 10.2 mmol) in ether (100 mL) was added DBU (6.8 g, 45.3 mmol). After the reaction mixture was stirred for 24 h at room temperature under a nitrogen atmosphere, it was washed with H_2O and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a silica gel column (hexane:ethyl acetate = 2:3) to give **7** (2.6 g, 76%) as a slightly yellow oil: IR (neat) 2960, 2930, 2852, 1667, 1382 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3H, $J = 6.7$ Hz, $–CH_3$), 1.22–1.54 (s, 20H, $–(CH_2)_{10}–$), 1.37 (s, 3H, acetonide), 1.55 (s, 3H, acetonide), 2.12 (t, 2H, $J = 7.5$ Hz, $–CH_2$), 4.89 (t, 1H, $J = 2.3$ Hz, C_2-H), 5.25 (m, 1H, C_3-H), 6.01 (d, 1H, $J = 5.3$ Hz, C_1-H).

5,6-Dideoxy-1,2-isopropylidene-5-*C*-(*n*-undecanyl)-α-D-galactofuranose (9). To a solution of 2-methyl-2-butene (5.5 mL, 5.02 mmol) in anhydrous THF (5 mL) was added dropwise borane-disulfide complex (1.25 mL of 2.0 M solution in THF, 2.5 mmol) with a syringe under a nitrogen atmosphere at 0 °C. After the mixture was stirred for 2 h at 0 °C, the solution of **8** (390 mg, 1.3 mmol) in THF (20 mL) was added dropwise to the mixture. The reaction mixture was stirred for 24 h at room temperature and then H_2O_2 (0.42 mL, 4.0 mmol) was carefully added at 0 °C. The reaction mixture was stirred for 24 h again at room temperature and then quenched with sodium sulfite. The reaction mixture was filtered and the organic solvent was removed. The aqueous layer was extracted with ether (3×20 mL). The etherate was dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a silica gel column (hexane:ethyl acetate = 1:2) to give **8** (210 mg, 50%) as a white solid: mp 52–53 °C; $[\alpha]^{20}_D = -22.3°$ (c = 6.9,

$CHCl_3$); IR (KBr) 3430 (–OH), 2930, 2850 1464, 1379 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3H, $J = 6.9$ Hz, $–CH_3$), 1.22–1.51 (m, 22H, $(CH_2)_{11}$–), 1.33 (s, 3H, acetonide), 1.62 (s, 3H, acetonide), 1.81 (d, 1H, $J = 4.4$ Hz, –OH), 3.92 (m, 1H, C_4-H), 4.11 (dd, 1H, $J = 3.9$, 7.9 Hz, C_3-H), 4.52 (d, 1H, $J = 3.9$ Hz, C_2-H), 5.91 (d, 1H, $J = 3.9$ Hz, C_1-H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26,2, 26.4, 27.1, 29.5, 29.6, 32.1, 33.9, 79.1 (C_4), 87.6 (C_2), 87.9 (C_3), 105.5 (C_1), 112.7 (C_7).

(2*S*,3*S*)-2-Benzyloxy-3-formyloxy-1-pentadecanal (4c). The same sequence of the reactions described for the synthesis of **4b** was applied. Benzylation of **9** (200 mg, 0.61 mmol) followed by the removal of the isopropylidene group gave the 1,2-*O*-diol compound (130 mg, 62%) as a white solid: mp 53–54 °C; IR (KBr) 3370, 3030, 29200, 2850, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, $J = 6.8$ Hz, $–CH_3$), 1.12–1.57 (m, 22H, $–(CH_2)_{11}$–), 1.62 (m, 1H, –OH), 3.81 (m, 1H, C_3-H), 4.21 (m, 2H, C_4-H), 4.61–4.81 (m, 3H, $–OCH_2$ and C_2-H), 5.31 (m, 1H, C_1-H), 7.33 (s, 5H, phenyl). Oxidative cleavage reaction of the 1,2-*O*-diol compound afforded **4c** (100 mg, 58%) as a slightly yellow oil: $[\alpha]^{20}_D = -24.3°$ (c = 39.1, $CHCl_3$); IR (neat) 3050, 2960, 2830, 1780 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3H, $J = 6.9$ Hz, $–CH_3$), 1.26 (s, 20H, $–(CH_2)_{10}$–), 1.68 (m, 2H, $–CH_2$), 3.88 (d, 1H, $J = 3.1$ Hz, C_2-H), 4,65 (s, 2H, $–OCH_2$), 5.39 (m, 1H, C_3-H), 7.35 (s, 5H, -phenyl), 8.05 (s, 1H, –OCHO), 9.66 (d, 1H, $J = 1.8$ Hz, –CHO); ^{13}C NMR ($CDCl_3$) δ 15.5, 24.1, 26.5, 30.7, 31.4, 33.3, 73.8 (C_3), 74.8 ($–OCH_2$), 84.1 (C_2), 129.5, 129.7, 130.0, 13 7.9, 162.1 (–OCHO), 202.4 (–CHO).

Ethyl (4*R*,5*S*)-4-benzyloxy-5-hydroxy-(2*E*)-heptadecanoate (5c). 4c (300 mg, 0.91 mmol) was subjected to the same reaction described for the synthesis of **5a**. **5c** (240 mg, 63%) was obtained as a slightly yellow oil: IR 3470 (–OH), 3030, 2920, 2860, 1721 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$) 0.89 (t, 3H, $J = 6.8$ Hz, $–CH_3$), 1.21–1.52 (m, 25H, $–(CH_2)_{11}$– and $–CH_3$), 2.11 (d, 1H, $J = 3.1$ Hz, –OH), 3.81 (m, 1H, C_5-H), 3.93 (m, 1H, C_4-H), 4.21 (q, 2H, $J = 4.6$ Hz, $–CO_2CH_2$–), 4.37–4.72 (dd, 2H, $J = 11.7$, 50.3 Hz, $–OCH_2$), 6.08 (d, 1H, $J = 14.8$ Hz, C_2-H), 6.96 (dd, 1H, $J = 14.8$, 6.9 Hz, C_3-H), 7.36 (s, 5H, -phenyl).

(−)-(4*R*,5*S*)-5-Hydroxyheptadeca-4-nolide (1c). 5c (240 mg, 0.57 mmol) was subjected to the same reaction described for the synthesis of **1a** from **5a**. **1c** (130 mg, 50%) was obtained as a white solid: mp 70.5 °C; $[\alpha]^{20}_D = -13.6°$ (c = 5.0, $CHCl_3$); IR (KBr) 3430 (–OH), 2960, 2920, 1780 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, $J = 6.9$ Hz, $–CH_3$), 1.22–1.51 (s, 22H, $–(CH_2)_{11}$–), 2.08 (s, 1H, –OH), 2.10 −2.45 (m, 2H, C_3-H), 2.61 (m, 2H, C_2-H), 3.94 (m, 1H, C_5-H), 4.43 (ddd, 1H, $J = 3.0$, 7.1, 10.1 Hz, C_4-H); ^{13}C NMR ($CDCl_3$) δ 15.5, 22.4, 24.0, 24.8, 26.6, 30.0, 30.7, 30.9, 72.7 (C_5), 84.2 (C_4), 178.9 (C_1); Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.61; H, 11.43.

5,6-Dideoxy-1,2-isopropylidene-5-*C*-(n-undecanyl)-α-D-gulofuranose (10). 9 (400 mg 1.2 mmol) was subjected to the same reaction described for the synthesis of **7**. **10** (300 mg, 76%) was obtained as a white solid: mp 52 °C; $[\alpha]^{20}_D = -2.5°$ (c = 0.65, $CHCl_3$); IR (KBr) 3472 (–OH), 2930, 2850 1464, 1379 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, $J = 6.8$ Hz, $–CH_3$), 1.24–1.49 (m, 22H, $–(CH_2)_{11}$–), 1.41 (s, 3H, acetonide), 1.62 (s, 3H, acetonide), 2.57 (d, 1H, $J = 7.4$ Hz, –OH), 3.86 (m, 1H, C_4-H), 4.18 (dd, 1H, $J = 5.7$, 11.8 Hz, C_3-H), 4.62 (dd, 1H, $J = 4.2$, 5.9 Hz, C_2-H), 5.66 (d, 1H, $J = 4.2$ Hz, C_1-H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 26.1, 26.9, 29.1, 29.6, 32.9, 70.2 (C_4), 80.2 (C_2), 82.5 (C_3), 101.5 (C_1), 111.5 (C_7).

(2*R*,3*S*)-2-Benzyloxy-3-formyloxy-1-pentadecanal (4d). The same sequence of the reactions described for the synthesis of **4b** was applied. Benzylation of **10** (300 mg, 0.91 mmol) followed by the removal of the isopropylidene group gave 1,2-*O*-diol compound (130 mg, 56%) as a white solid: IR (neat) 3350, 3060, 2920, 2850, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, $J = 6.8$ Hz, $–CH_3$), 1.14–1.60 (m, 22H, $–(CH_2)_{11}$–), 1.65 (m, 1H, –OH), 3.91 (m, 1H, C_3-H), 4.15 (m, 2H, C_4-H), 4.61–4.83 (m, 3H, $–OCH_2$ and C_2-H), 5.08 (m, 1H, C_1-H), 7.33 (s, 5H, -phenyl). Oxidative cleavage reaction of the 1,2-*O*-diol compound afforded **4d** (160 mg, 47%) as a slightly yellow oil: $[\alpha]^{20}_D = +20.2°$ (c = 10.0, $CHCl_3$); IR (neat) 3050, 2920, 2846, 1739 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, $J = 6.9$ Hz, $–CH_3$), 1.25 (s, 20H, $–(CH_2)_{10}$–), 1.75 (m, 2H, $–CH_2$), 3.88 (dd, 1H, $J = 1.6$, 3.6 Hz, C_2-H), 4.53–4.82 (dd, 2H, $J = 11.8$, 49.6 Hz, $–OCH_2$), 5.28 (m, 1H, C_3-H), 7.35 (s, 5H, -phenyl), 8.05 (s, 1H, –OCHO), 9.66 (d, 1H, $J = 1.4$ Hz, –CHO); ^{13}C NMR ($CDCl_3$) δ 20.9, 25.4, 29.5, 29.7, 30.3, 32.1, 72.7 (C_3), 76.1 ($–OCH_2$), 84.0 (C_2), 128.5, 128.8, 129.0, 129.9, 160.3 (–OCHO), 201.2 (–CHO).

Ethyl (4*S*,5*S*)-4-benzyloxy-5-hydroxy-(2*E*)-heptadecanoate (5d). 4d (200 mg, 0.53 mmol) was subjected to the same reaction described for the synthesis of **5b**. **5d** (140 mg, 62%) was obtained as a slightly yellow oil. IR (neat) 3460 (–OH), 3070, 2920, 2860, 1721 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, $J = 6.8$ Hz, $–CH_3$), 1.21–1.52 (m, 25H, $–(CH_2)_{11}$– and $–CH_3$), 2.52 (m, 1H, –OH), 3.58 (m, 1H, C_5-H), 3.81 (m, 1H, C_4-H), 4.23 (q, 2H, $J = 4.6$ Hz, $–CO_2CH_2$–), 433–4.72 (dd, 2H, $J = 11.9$, 49.9 Hz, $–OCH_2$), 6.10 (d, 1H, $J = 14.8$ Hz, C_2-H), 6.96 (dd, 1H, $J = 14.8$, 6.8 Hz, C_3-H), 7.36 (s, 5H, -phenyl).

(+)-(4*S*,5*S*)-5-Hydroxyheptadeca-4-nolide (1d). 5d (140 mg, 0.34 mmol) was subjected to the reaction described for the synthesis of **1a**. **1d** (50 mg, 52%) was obtained as a

white solid: mp 72.0 °C, lit.[2c] 73–74 °C, lit.[2a] 65 °C; $[\alpha]^{20}_{D} = +16.9°$ (c = 6.5, $CHCl_3$), lit.[2c] +23.02° (c = 1.26, $CHCl_3$), lit.[2a] +25° (c = 1.7, MeOH); IR (KBr) 3390 (–OH), 2917, 2910, 1745 (C = O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, $J = 6.9$ Hz, $–CH_3$), 1.20–1.51 (s, 22H, $–(CH_2)_{11}–$), 1.82 (s, 1H, –OH), 2.22 (m, 2H, C_3-H), 2.51 (ddd, 2H, $J = 5.6$, 10.1, 12.7 Hz, C_2-H), 3.51 (m, 1H, C_5-H), 4.44 (ddd, 1H, $J = 3.0$, 7.0, 10.1 Hz, C_4-H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 24.1, 25.5, 28.7, 29.4, 31.9, 33.0, 73.7 (C_5), 82.9 (C_4), 177.0 (C_1); Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.57; H, 11.64.

Cytotoxicity assay

Cytotoxicities (SRB assay) against in vitro A-549 and MCF-7 cell lines were determined at the Choong-Wae Pharmaceutical Company, LTD., Korea, according to the procedure described by Skehan et al.[12]

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