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Original article

Total synthesis and anticancer activity of highly potent novel glycolipid derivatives

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ABSTRACT

The total synthesis and anticancer activity of several novel derivatives based on a dauer effect-inducing glycolipid are presented. A versatile and convergent synthesis was accomplished through stereospecific α-glycosylation, which produced di- and tri-rhamnoside daumone derivatives. Most of the synthetic derivatives possessed potent anticancer activity against human cancer cell lines. Daumone and deoxy-rhamnose trisaccharides with amide side chains had the most potent anticancer activity among all other known glycolipids, with an effective concentration of 20 nM, which is comparable to that of doxorubicin. Conversely, acyclic and macrocyclic daumone derivatives had drastically decreased anticancer activity. Due to the high lipophilic nature of the novel glycolipid derivatives, we propose that the observed anticancer activity is due to their potential to inhibit cell differentiation and proliferation via interaction with the membranes of cancer cells.

1. Introduction

Glycolipids are ubiquitous membrane constituents of animals and plants that have attracted broad interest in the last few decades due to their important roles as cell-surface-associated antigens and recognition factors [1] Glycolipids fractioned from spinach have been shown to inhibit the activities of replicative DNA polymerase (pols) and mitochondrial pol [2,3], raising the possibility of using glycolipids as anticancer chemotherapeutic agents. Due to their highly lipophilic nature, glycolipids could be further developed into anticancer drug candidates due to their ability to interact with the lipid membrane and inhibit cell proliferation [4].

Although some studies have reported interesting glycolipid anticancer activity, the relatively weak activity of this class of compounds has generally discouraged further investigation [4–10]. Recently, our laboratory identified a glycolipid (**1**) as a dauer-inducing pheromone (dauer: a German word meaning "enduring" and is used to describe an alternative developmental stage of nematodes) from *Caenorhabditis elegans* which is able to extend their lifespan by 10 times [11]. In continuation of the investigation of additional biological activities of this new glycolipid, we report a versatile synthesis of novel glycolipid derivatives and study their potent anticancer activity against human cell lines through a structure–activity relationship. Diversity in structure based on the daumone will help design to find more potent anticancer glycolipids. A possible mode of action to explain the anticancer activity of the novel glycolipid derivatives is also proposed.

2. Results and discussion

2.1. Chemistry

In order to investigate the structure–anticancer activity relationship (SAR) of the lead compound daumone **1**, a versatile synthesis of novel glycolipid derivatives **2**–**3**, **8**–**10**, **14**–**15**, **17**, and **20**–**22** was performed as described in Schemes 1–4. Coupling of the carboxy group of daumone with diverse functional groups (amines or alcohols), as well as glycosylation of the 2′- and/or 4′-hydroxy groups of 3-deoxy L-rhamnose with a monosaccharide afforded new glycolipid mono-, di-, and tri-rhamnosides for anticancer activity testing.

Although some of the glycolipids were prepared in poor yield, we chose to give priority to the preparation of new compounds; additional optimization will be performed in due course. First, the lead glycolipid (**1**) was prepared as described previously in a 10-step synthesis beginning with commercially available L-rhamnose [11]. Coupling of the fatty carboxy group of compound **1** with various amines (amidation with *n*-tetradecyl amine, 4-ethylaniline,

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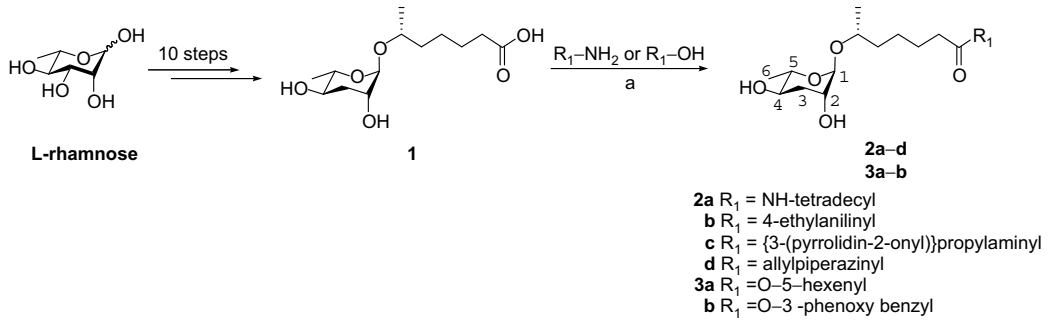
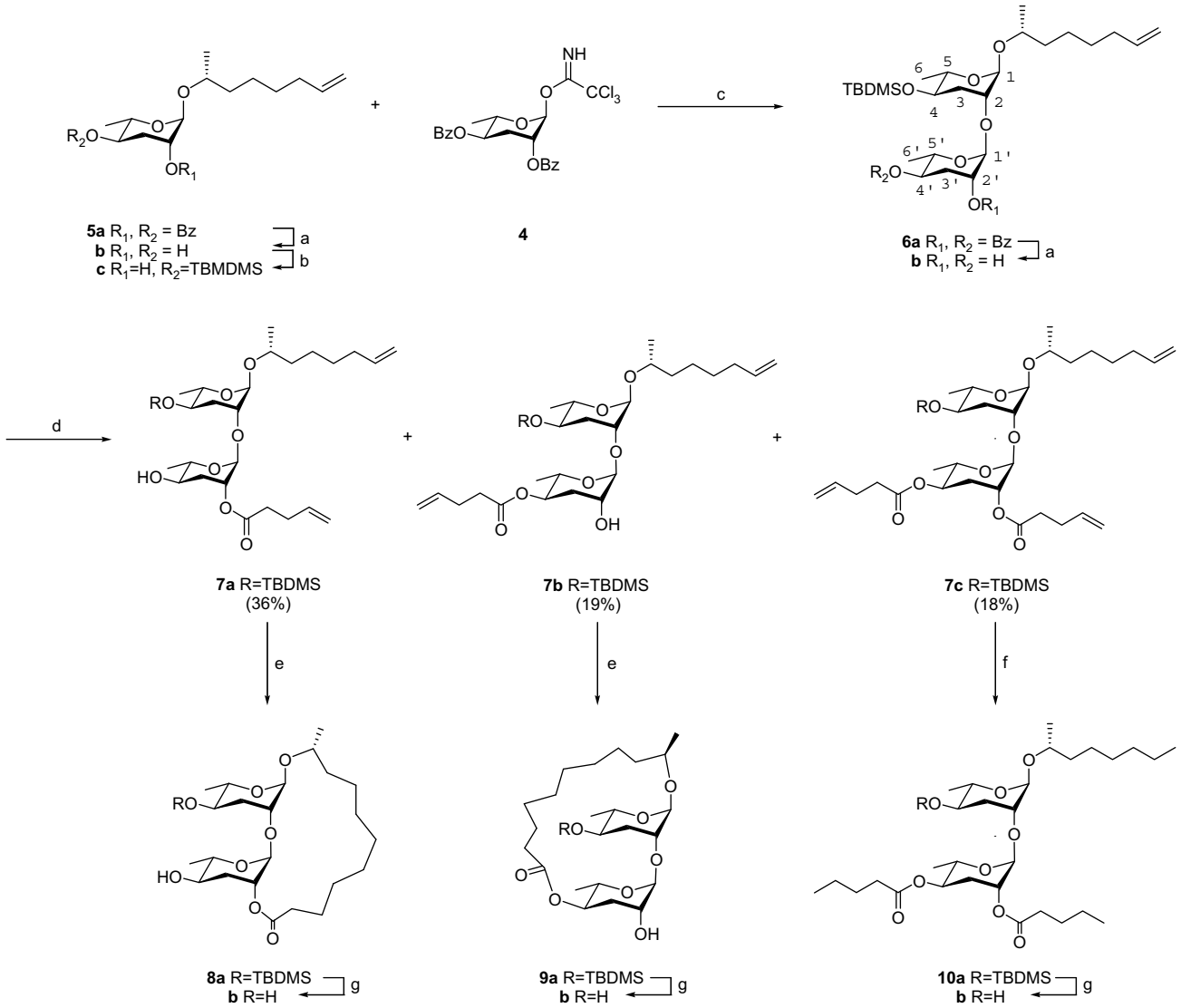


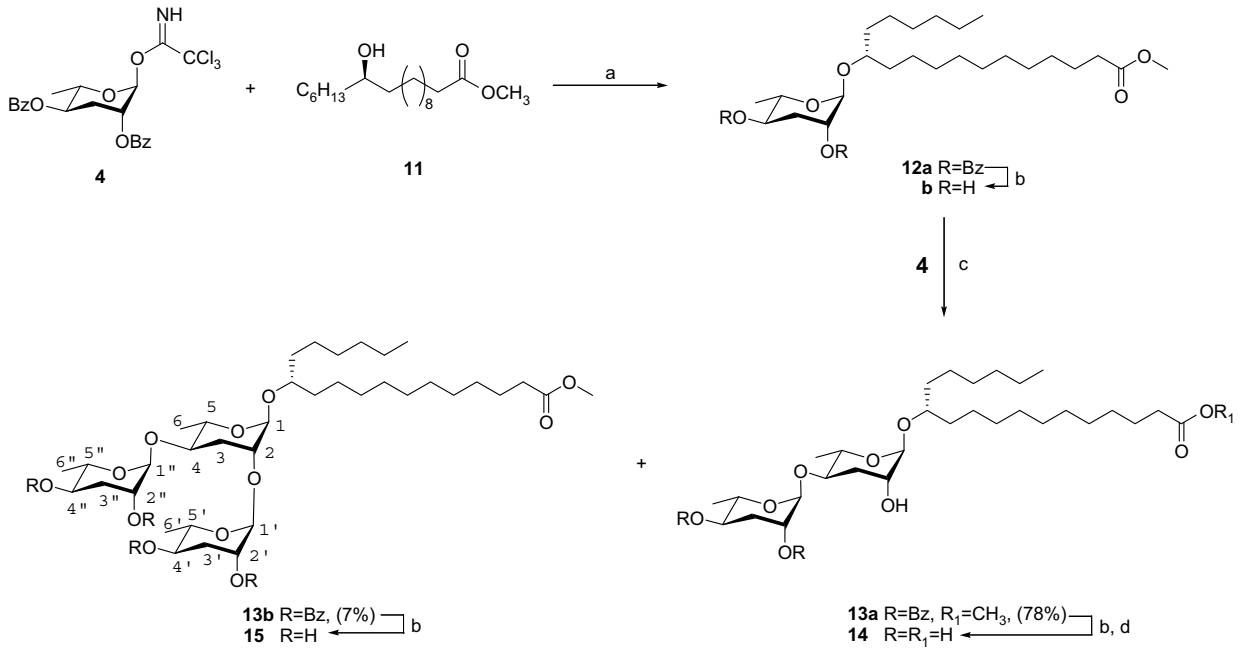
Scheme 1. Synthesis of new derivatives of amides and esters prepared from dauer pheromone **1**. [a] Reagents and conditions: (a) amines; (tetradecylamine, 4-ethylaniline, (3′-aminopropyl)-2-pyrrolidinone, or allylpiperazine), alcohols; (5-hexen-1-ol, or 3-phenoxy benzyl alcohol), EDC, HOBt, DMF, room temp., 3–5 h.

(3′-aminopropyl)-2-pyrrolidinone, allylpiperazine) and alcohols (esterification with 5-hexen-1-ol, 3-phenoxy benzyl alcohol) afforded the amides **2a**–**d** and **3a**–**b** in yields of 55–79% and 30–35%, respectively (Scheme 1). For amidation and esterification of compound **1**, direct coupling without protection of secondary 2′ and 4′ hydroxyl groups gave amides and esters in the better yields than with benzoyl protecting groups at 2′ and 3′ positions.

A versatile and convergent synthesis of di- and tri-rhamnoside daumone derivatives was accomplished through stereospecific α-glycosylation via a key step as described in Schemes 2–4.

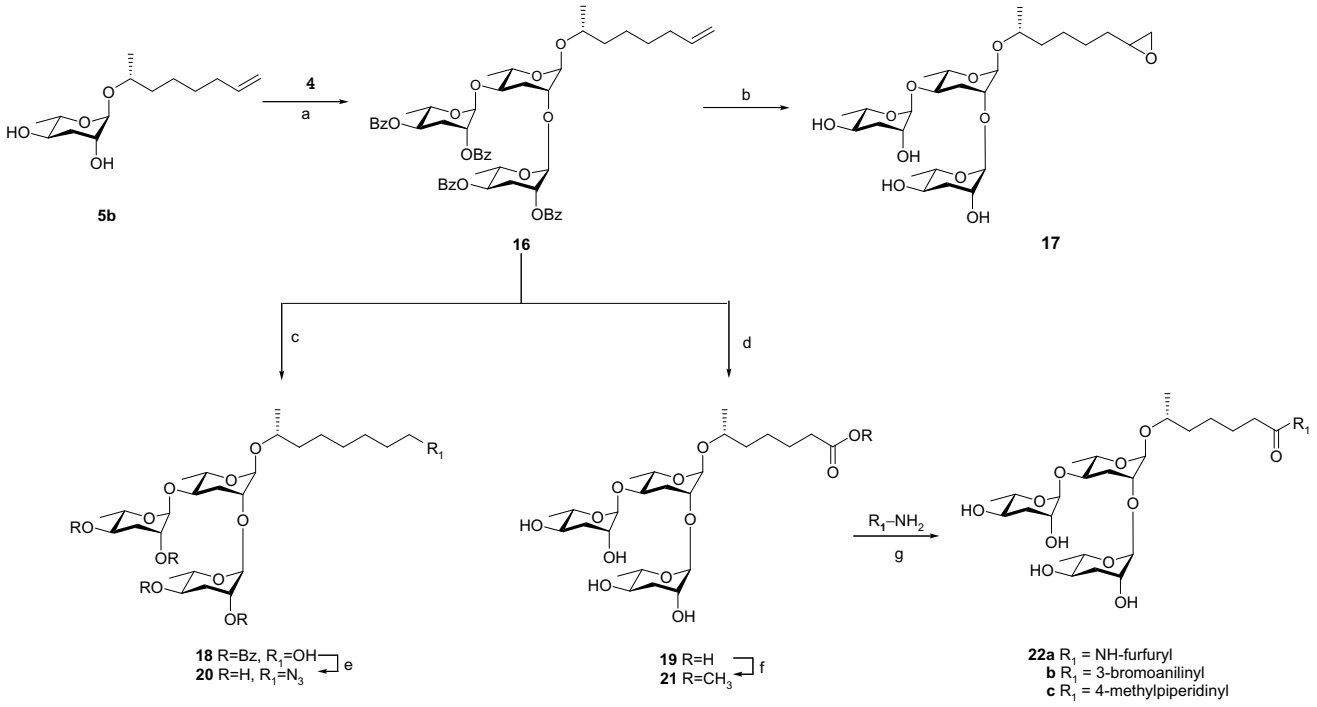


Scheme 2. Preparation of novel di-rhamnoside daumone derivatives and their cyclic analogues. [a] Reagents and conditions: (a) NaOMe, MeOH, 0 °C to room temp., 8 h; (b) TBDMSCl, imidazole, DMF, room temp., 3 h; (c) BF_3–OEt_2, CH_2Cl_2, −20 °C, 3 h; (d) 4-pentenoic acid, EDC, HOBt, toluene, reflux (110–120 °C), 24 h; (e) (i) Grubbs second-generation Ru cat., toluene, reflux (110–120 °C), 20 h; (ii) Pd/C, H_2, EtOH, 0 °C, 12 h; (f) Pd/C, H_2, EtOAc, 0 °C, 5 h; (g) HF/pyridine, pyridine, room temp., 12 h.



Scheme 3. Preparation of di- and tri-rhamnoside daumone derivatives with long hydrophobic side chains. [a] Reagents and conditions: (a) 1 M $SnCl_4$, CH_2Cl_2, −78 °C, 5 h; (b) NaOMe, MeOH, 0 °C to room temp., 8 h; (c) BF_3–OEt_2, CH_2Cl_2, −20 °C, 3 h; (d) (i) NaOMe, MeOH, 0 °C to room temp., 8 h; (ii) 10% NaOH, THF/H_2O, room temp., 5 h.

Deprotection (89% yield) at C-2 and C-4 of the known intermediate **5a** [11] produced compound **5b**, and following regioselective silylation (89%) of the C-4 hydroxyl group of compound **5b** with *tert*-butyldimethylsilyl chloride in the presence of imidazole in DMF (room temp.), compound **5c** (71%) was produced. Glycosylation of donor **4** with acceptor **5c** was achieved in the presence of BF_3–OEt_2 [12] in CH_2Cl_2 at −20 °C to give disaccharide **6a** at a 94% yield with a natural α-configuration exclusively at C-1 of the known donor **4** [13]. The high stereoselectivity achieved in the glycosylation using boron trifluoride was attributed to the neighboring group effect of the C-2 substituent of compound **4** *via* formation of an acyloxonium ion with concomitant stabilization of the positive charge on C-1



Scheme 4. Preparation of novel tri-rhamnoside derivatives of pheromone **1**. [a] Reagents and conditions: (a) compound **4**, TMSOTf, CH_2Cl_2, −20 °C, 5 h; (b) (i) NaOMe, MeOH, 0 °C to room temp., 8 h; (ii) *m*-CPBA, CH_2Cl_2, 0 °C, 24 h; (c) 0.5 M 9-BBN, H_2O_2, 3 N NaOH, room temp., 2 h; (d) (i) $NaIO_4$, $RuCl_3 \cdot H_2O$, $CH_2Cl_2/CH_3CN/H_2O$, room temp., 4 h; (ii) NaOMe, MeOH, 0 °C to room temp., 8 h; (e) (i) TsCl, Et_3N, CH_2Cl_2, 0 °C to room temp., 4 h; (ii) NaN_3, DMF, room temp., 8 h; (iii) NaOMe, MeOH, 0 °C to room temp., 8 h; (f) *p*-TsOH, MeOH, 0 °C, 14 h; (g) amines; (furfurylamine, 3-bromoaniline, or 4-methylpiperidine) EDC, DMAP, DMF, room temp., 24 h.

[14a,b]. Structural assignment of the α-L-rhamnopyranoside was further confirmed by the chemical shift of the two anomeric carbons (δ 95.5 and 95.0) and lack of coupling contacts of the anomeric protons (δ 4.93 and 4.87) for **6a**, in agreement with previous findings [15a,b,16]. Selective removal of the benzoate protecting groups of compound **6a** using NaOMe in dry MeOH afforded compound **6b** in excellent yield (93%). Esterification of the hydroxyl group at C-2′ of the di-rhamnoside daumone derivative **6b** with 4-pentenoic acid in the presence of EDC and HOBt in toluene (reflux, 24 h) gave the di-rhamnoside daumone esters **7a** (36%), **7b** (19%), and **7c** (18%), respectively (Scheme 2). Macrocyclization via ring-closing metathesis (RCM) of the separated di-rhamnoside daumone esters **7a**–**b** in the presence of Grubbs 2nd Ru reagent [17] successfully afforded novel macrocyclic glycolipids **8a** and **9a** in 21% and 15% yields, respectively; these were identified as potential pharmacophores. Removal of the protective TBDMS group at C-4 of **8a** and **9a** by HF/pyridine (pyridine, room temp., 12 h) cleanly provided **8b** (15%) and **9b** (12%), respectively. Hydrogenation (Pd/C, H_2, EtOAc, 0 °C, 5 h) of all three alkenyl side chains of **7c** gave the hydrogenated di-rhamnoside daumone derivative **10a** (91%), which was subjected to the same deprotection as that of compound **8a** to give **10b** (78%) (Scheme 2).

Coupling of the intermediate **4** with the fatty hydroxyester side long chain **11** afforded compound **12a** in a 74% yield. Subsequent deprotection of C-2, 4 of compound **12a** gave monomer **12b** in a 95% yield (Scheme 3). The α-configuration of the new glycosidic bond in monomer **12a** was confirmed by absence of coupling constant of the anomeric proton at δ 4.93 and chemical shift of the anomeric carbons at δ 95.4. The stereoselective α-glycosylation in the presence of BF_3–OEt_2 (CH_2Cl_2, −20 °C, 3 h) at C-4 and C-2 of **12b** with compound **4** afforded the di-rhamnoside daumone derivative **13a** (79%) and the tri-rhamnoside derivative **13b** (7%), respectively. Similarly, the α-configuration of **13a** and **13b** was assigned on the basis of the lack of a coupling constant of the anomeric proton at δ_H 4.97, 4.85 (**13a**), protons δ_H 5.07, 5.00, 4.92 (**13b**), and chemical shift of the anomeric carbons at δ 96.7, 95.4 (**13a**) and δ 96.7, 95.8, 92.9 (**13b**), respectively. Deprotection of compound **13a** using NaOMe in dry MeOH at 0 °C and then 10% NaOH (THF/H_2O, room temp., 8 h) provided compound **14** in a 51% yield. Deprotection of compound **13b** gave **15** in a 64% yield (Scheme 3).

Coupling of glycolipid **5b** with excess intermediate **4** in the presence of TMSOTf at 0 °C afforded trimer **16** in an 85% yield via stereospecific α-glycosylation (Scheme 4). The α-configuration of the fully protected α-glycoside **16** was assigned on the basis of a lack of a coupling constant of the anomeric proton at δ 5.06 (2H, donor) and 4.94 (1H, acceptor). In addition, the three anomeric carbons of α-glycoside **16** were confirmed at δ 96.0, 94.9, and 93.0, respectively. Deprotection of the *O*-benzoyl groups of the sugars of compound **16** with NaOMe in 94% yield and epoxidation with *m*-CPBA gave compound **17** in a 50% yield. Oxidative hydroboration (9-BBN, H_2O_2/3 N NaOH) of **16** to give hydroxyl **18** in 76% yield, along with subsequent azidation with NaN_3 gave the azide **20** in a 96% yield (Scheme 4). Compound **21** was prepared from protected **16** by oxidation of the terminal double bond with $NaIO_4$ and $RuCl_3$, which gave a 71% yield, and deprotection with NaOMe following final methylation of compound **19** with *p*-TsOH gave free tri-rhamnoside daumone derivative **21** in a 47% yield. Although amidation of unprotected compound **19** with *N*,*N*′-dicyclohexylcarbodiimide (DCC) as a coupling agent in the presence DMAP as previously reported [18] gave **22a**–**c** in good yields, removal of the byproduct *N*,*N*-dicyclohexylurea (DCU) was difficult. Thus, this problem was simply resolved by replacement of DCC to 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) [19] as a clean dehydrating agent with DMAP in DMF (room temp., 24 h). The possible amidation of the unprotected secondary hydroxyl groups of the rhamnose residues with the amines especially in view of the use of DMAP in the coupling reaction was not detected. Finally, amidation of unprotected compound **19** cleanly afforded amides, **22a** (47% yield), **22b** (76% yield), and **22c** (58% in yield) (Scheme 4).

2.2. Anticancer activity (SAR)

The *in vitro* cytotoxicity of synthetic glycolipids and its related derivatives against human cancer cells lines of the lung (A549), ovary (SK-OV-3), brain (XF498), and the colon (HCT15), as well as a melanoma line (SK-MEL-2) was determined by sulforhodamin B (SRB) assay [20]. The IC_{50} values are presented in Table 1.

Most synthetic derivatives of glycolipids possessed potent anticancer activity against human cancer cell lines. In addition to extending the lifespan of *C. elegans* by 10 times, daumone **1** exhibited very strong anticancer activity against human lung cancer cells, adenocarcinoma cells, and colon carcinoma cells, all of which were comparable to that of doxorubicin. In addition, daumone **1** was two times more potent than doxorubicin against human CNS tumors. Further, we determined that the deoxo-rhamnose sugar moiety on the aliphatic side chain was essential for tumor-regression activity.

Derivatization of side chains of compound **1** as amides **2a**–**d**, and esters **3a**–**b** drastically decreased the anticancer activity observed above by four to ten times compared to that of daumone **1**. Among amide derivatives, aliphatic side chain (**2a**) or aromatic (**2b**) moiety enhanced the anticancer activity 3 times than heterocycle moiety (**2c**, **2d**). Cyclic and acyclic di-rhamnoside daumone derivatives **8b**, **9b** and **10b**, **14**, respectively, exhibited significantly decreased anticancer activity as well. The shapes of the cyclic derivatives **8b** and **9b**, with two sugar moieties and rigid macrocycle were due to the connection of the terminal fatty side chain, which possibly inhibited the approach of the derivatives into the putative receptor responsible for the observed inhibition of cancer cell proliferation, resulting in relatively low activity of the two cyclic derivatives.

Table 1
In vitro anticancer activity of novel glycolipid derivatives **2a**–**22c**.

Compound	IC_{50} (μg/mL)[a]				
	A549[b]	SK-OV-3[c]	SK-MEL-2[d]	XF498[e]	HCT15[f]
2a	0.16	0.24	0.11	0.42	0.31
2b	0.34	0.24	0.11	0.25	0.2
2c	0.76	0.65	0.33	0.25	0.54
2d	0.54	0.32	0.53	0.62	0.34
3a	0.12	0.31	0.22	0.15	0.12
3b	0.24	0.54	0.13	0.52	0.75
8b	0.57	0.14	0.44	0.43	0.54
9b	0.63	0.73	0.33	0.34	0.65
10b	0.78	0.73	0.43	0.45	0.21
14	0.64	0.32	0.33	0.43	0.53
15	0.12	0.24	0.32	0.32	0.1
17	0.76	0.14	0.65	0.65	0.21
20	0.24	0.14	0.33	0.43	0.14
21	0.13	0.14	0.41	0.19	0.21
22a	0.08	0.01	0.04	0.07	0.06
22b	0.07	0.07	0.09	0.05	0.02
22c	0.06	0.03	0.03	0.06	0.02
1 Daumone[g]	0.03	0.02	0.07	0.09	0.05
Doxorubicin[h]	0.04	0.024	0.015	0.19	0.02

[a] IC_{50}: concentration that produces 50% inhibition of proliferation after 72 h of incubation.
[b] A549: human lung carcinoma (tumor).
[c] SK-OV-3: human adenocarcinoma (tumor), malignant ovary ascites.
[d] SK-MEL-2: human malignant melanoma, metastasis to skin of thigh.
[e] XF498: human central nerve system tumor (brain tumor).
[f] HCT15: human colon adenocarcinoma (tumor).
[g] A control material.
[h] A standard material.

Three novel trisaccharides, deoxyrhamnose derivatives **22a–c** of compound **1** containing an amide side chain, exhibited the most potent anticancer activity (Table 1), with an effective concentration of 20 nM, which was comparable to that of doxorubicin in our *in vitro* cytotoxicity results against human A549, SK-OV-3, SK-MEL-2, XF498 and HCT15 cells. Of all known glycolipids, these derivatives possessed the most potent active anticancer activity in 20 nM compared with that ($IC_{50} = 7–12$ μM against human cancer cells) of the previously known glycolipids [10]. It is noteworthy that the aliphatic terminal modification into epoxide **17**, azide **20**, ester **21** of side chain of the above mentioned tri-rhamnoside daumone derivatives significantly decreased, by 5- to 10-fold, the activity of daumone **1**. Since trisaccharides **22a–c** with amide side chains were the most active against human cancer cell lines, we hypothesized that incorporation of additional saccharide functional groups into the di-rhamnoside derivatives would further increase the anticancer activity. Although no activity difference was found among trisaccharide amides (**22a–c**) with different side chains, the trimers showed 5–10 times more anticancer activity than that of monomer amides (**2a–d**). In general, the presence of the amide bond of the fatty side chain of **22a–c** enhanced the activity while the presence of a macrocyclic system without amide groups in the cyclic di-rhamnoside **8** and **9** decreased the anticancer activity. These findings suggest that the amide side chain on the tri-rhamnoside sugars is the structure principally responsible for establishing the most active anticancer activity.

2.3. Mechanism of anticancer activity

Elucidation of the mechanism of anticancer action of these novel derivatives would help to explain the observed differences in activity between the structurally diverse derivatives and help guide the design of more effective anticancer drugs. The glycolipid derivatives were made to assess their potential to inhibit differentiation and proliferation of cancer cells. It is not known if glycolipids interact with calmodulin, an intracellular Ca^{2+} binding protein, which is essential for cell proliferation [21]. In preliminary testing, the glycolipid derivatives did not show any histone deacetylation inhibition activity.

Although details of the mechanism of apoptosis remain unclear, lipophilicity may play an important role in glycolipid anticancer activity. The relative lipophilicity of these compounds could obviously determine the quantities that accumulate in the membrane; however, since the exposed tri-rhamnoside daumone derivative backbone with polyhydroxy groups would render the amides **22a–c** more polar than mono- and di-rhamnoside daumone derivatives, the higher cytotoxicity of compounds **22a–c** is probably related to the extent of incorporation into the membranes of sensitive cells [10]. The differences in activity of both series of di- and tri-rhamnoside daumone derivatives, particularly from the point of view of hydrophilicity, could be explained if both series have different targets or different modes of action [4].

The cell-inhibitory profile of the amide-linked glycolipids strengthens the hypothesis that such glycolipids represent a distinct group of antitumor amide lipids, having antineoplastic activities that differ from the well-known alkylphosphocholines and alkylphospholipids [10].

3. Conclusion

The total synthesis and anticancer activity of novel derivatives based on dauer effect-inducing glycolipids are presented. A versatile and convergent synthesis was accomplished through stereospecific α-glycosylation to afford both di- and tri-rhamnoside daumone derivatives. Most synthetic derivatives possessed potent anticancer activity against human cancer cell lines. Daumone and its tri-deoxyrhamnose derivatives containing amide side chains were the most potent anticancer compounds, with effective concentrations in the nanomolar range, which is comparable to that of doxorubicin; acyclic and cyclic di-rhamnoside daumone derivatives exhibited drastically decreased anticancer activity. Due to the highly lipophilic nature of tri-rhamnoside daumone derivatives of glycolipids, we propose a possible mode of action to explain the observed anticancer activity, whereby the glycolipids inhibit cell differentiation and proliferation by interacting with the membrane of cancer cells.

4. Experimental section

4.1. Chemistry

All commercial reagents and solvents were used as received without further purification unless specified. Reaction solvents were distilled from calcium hydride for dichloromethane and from sodium metal and benzophenone for tetrahydrofuran. The reactions were monitored and the R_f values were determined using analytical thin layer chromatography (TLC) with Merck silica gel 60 and F-254 precoated plates (0.25-mm thickness). Spots on the TLC plates were visualized using ultraviolet light (254 nm) and a basic potassium permanganate solution or cerium sulfate/ammonium dimolybdate/sulfuric acid solution followed by heating on a hot plate. Flash column chromatography was performed with Merck silica gel 60 (230–400 mesh). ^{1}H NMR spectra were recorded on Bruker DRX-250 or Bruker DRX-400 NMR spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.00) or with the solvent reference relative to TMS employed as the internal standard ($CDCl_3$, δ 7.26 ppm; d_4-CD_3OD, δ 3.31 ppm). Data were reported as follows: chemical shift {multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration}. ^{13}C NMR spectra were recorded on Bruker DRX-250 (62.9 MHz) or Bruker DRX-400 (100.0 MHz) NMR spectrometers with complete proton decoupling. Carbon chemical shifts were reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.0 ppm; d_4-CD_3OD, δ 49.0 ppm). Infrared (IR) spectra were recorded on a Nicolet Model Impact FT-IR 400 spectrometer; data are reported in wave numbers (cm^{-1}). High resolution mass spectrometer (HRMS) analyses were recorded on an Applied Biosystems 4700 proteomics analyzer spectrometer. Specific rotations were recorded on a Rudolph AP III-589 polarimeter.

4.2. General procedure for preparation of daumone esters and amides (*2a–2d* and *3a–3b*)

A stirred solution of acid **1** (20 mg, 0.07 mmol), HOBt (30 mg, 0.62 mmol), and EDC (45 mg, 0.62 mmol) in DMF (2 mL) was combined with the appropriate amines (0.08 mmol) (tetradecylamine for compound **2a**, 4-ethylaniline for compound **2b**, (3′-aminopropyl)-2-pyrrolidinone for compound **2c**, and allylpiperazine for compound **2d** or alcohols (0.08 mmol) (5-hexen-1-ol for compound **3a**, and 3-phenoxy benzyl alcohol for compound **3b**) at room temperature, and the reaction mixture was stirred at same temperature for 3–5 h. The reaction mixture was quenched with slow addition of saturated citric acid (2 mL), extracted with ethyl acetate (3×20 mL) and washed with brine (2×10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product, which was further purified by flash silica gel chromatography using hexane/EtOAc/MeOH

(**2a**) and CH_2Cl_2/MeOH (**2b**–**d**, and **3a**–**b**) as eluents to afford pure amide and ester glycolipid derivatives.

*4.2.1. (6R)-(Tetradecyl heptanamide)-3-deoxy-α-L-rhamnopyranoside (**2a**)*

A colorless oil; yield, 79%; $R_f = 0.19$ (hexane/EtOAc/MeOH, 5:5:1); $[\alpha]_D^{20} = -49.1$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$); δ 7.96 (s, 1H, NH) 4.64 (s, 1H), 3.79–3.74 (m, 1H), 3.71 (s, 1H), 3.64–3.46 (m, 2H), 3.17–3.12 (m, 2H), 2.18 (t, 2H, $J = 7.4$ Hz), 1.98–1.90 (m, 1H), 1.81–1.70 (m, 1H), 1.64–1.56 (m, 2H), 1.54–1.41 (m, 6H), 1.29 (s, 22H), 1.19 (d, 3H, $J = 5.9$ Hz), 1.11 (d, 3H, $J = 6.1$ Hz), 0.92–0.87 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$); δ 176.0, 97.3, 72.1, 71.1, 69.9, 68.3, 38.1, 36.0, 33.1, 30.8, 30.7, 30.5, 30.4, 28.0, 27.1, 26.5, 23.8, 19.3, 18.2, 14.5; IR (film) ν_{max}; 3307, 2925, 2854, 1647, 1554, 1459, 1375, 1250, 1128, 1043, 984 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{27}H_{53}NO_5$ $[M+H]^+$ m/z, 472.4002; found, 472.4005.

*4.2.2. (6R)-(4-Ethylanilinyl heptanamide)-3-deoxy-α-L-rhamnopyranoside (**2b**)*

A colorless oil; yield, 66%; $R_f = 0.28$ (CH_3Cl/MeOH, 9:1); $[\alpha]_D^{20} = -97.0$ ($c = 0.05$, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$); δ 8.08 (s, 1H, NH), 7.43–7.08 (m, 4H), 4.68 (s, 1H), 3.77–3.70 (m, 2H), 3.66–3.52 (m, 2H), 3.15 (br s, 2H), 2.62–2.53 (m, 2H), 2.32 (t, 2H, $J = 7.1$ Hz), 2.06–2.01 (m, 1H), 1.88–1.78 (m, 1H), 1.70 (m, 2H), 1.46 (m, 4H), 1.28–1.15 (m, 6H), 1.08 (d, 3H, $J = 5.9$ Hz). ^{13}C NMR (63 MHz, $CDCl_3$); δ 172.0, 140.3, 135.7, 128.3, 120.3, 95.5, 70.6, 69.8, 69.2, 67.9, 37.6, 36.9, 35.2, 28.3, 25.8, 19.0, 17.9, 15.7; IR (film) ν_{max}; 3419, 2967, 2931, 1654, 1540, 1455, 1411, 1375, 1310, 1254, 1124, 1027 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{21}H_{33}NO_5$ $[M]^+$ m/z, 379.2359; found, 379.2354.

*4.2.3. (6R)-(3-(Pyrrolidin-2-onyl)propylaminyl heptanamide)-3-deoxy-α-L-rhamnopyranoside (**2c**)*

A colorless oil; yield, 58%; $R_f = 0.43$ (CH_2Cl_2/MeOH, 7:1); $[\alpha]_D^{20} = -33.0$ ($c = 0.10$, MeOH); ^{1}H NMR (250 MHz, MeOH); δ 4.63 (s, 1H), 3.81–3.77 (m, 1H), 3.74–3.70 (m, 1H), 3.66–3.53 (m, 2H), 3.51–3.44 (m, 2H), 3.30 (t, 2H, $J = 6.8$ Hz), 3.15 (t, 2H, $J = 6.9$ Hz), 2.38 (t, 2H, $J = 8.3$ Hz), 2.20 (t, 2H, $J = 7.5$ Hz), 2.08–2.02 (m, 2H), 2.02–1.92 (m, 1H), 1.80–1.69 (m, 3H), 1.66–1.55 (m, 3H), 1.51–1.38 (m, 3H), 1.20 (d, 3H, $J = 5.9$ Hz), 1.11 (d, 3H, $J = 6.1$ Hz). ^{13}C NMR (63 MHz, $CDCl_3$); δ 177.8, 176.1, 97.4, 72.2, 71.1, 69.9, 68.3, 48.7, 41.2, 38.1, 37.7, 37.1, 36.0, 32.0, 28.0, 27.0, 26.5, 19.3, 18.8, 18.1; IR (film) ν_{max}; 3386, 2927, 1649, 1548, 1495, 1467, 1442, 1377, 1292, 1127, 1044, 1029, 984 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{20}H_{36}N_2O_6$ $[M+H]^+$ m/z, 401.2652; found, 401.2656.

*4.2.4. (6R)-(Allylpiperazinyl heptanamide)-3-deoxy-α-L-rhamnopyranoside (**2d**)*

A colorless oil; yield, 55%; $R_f = 0.42$ (CH_2Cl_2/MeOH, 7:1); $[\alpha]_D^{20} = -84.3$ ($c = 0.07$, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$); δ 5.90–5.79 (m, 1H), 5.24–5.17 (m, 2H), 4.72 (s, 1H), 3.80–3.62 (m, 4H), 3.62–3.60 (m, 2H), 3.52–3.48 (m, 2H), 3.02 (d, 2H, $J = 6.5$ Hz), 2.46–2.30 (m, 6H), 2.12–2.05 (m, 1H), 1.90–1.86 (m, 1H), 1.70–1.56 (m, 2H), 1.51–1.37 (m, 4H), 1.28 (m, 3H), 1.13 (d, 3H, $J = 6.0$ Hz). ^{13}C NMR (63 MHz, MeOD); δ 174.0, 136.5, 119.5, 97.4, 72.2, 71.1, 69.9, 68.3, 62.3, 54.1, 53.6, 46.5, 42.4, 38.1, 36.0, 33.9, 26.6, 26.5, 19.3, 18.2; IR (film) ν_{max}; 3423, 2927, 1738, 1625, 1445, 1240, 1131, 1044, 1029, 985, 919, 448 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{20}H_{36}N_2O_5$ $[M+H]^+$ m/z, 385.2702; found, 385.2697.

*4.2.5. (6R)-(5-Hexenyl heptanoate)-3-deoxy-α-L-rhamnopyranoside (**3a**)*

A colorless oil; yield, 35%; $R_f = 0.40$ (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D^{20} = -94.0$ ($c = 0.05$, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$); δ 5.88–5.72 (m, 1H), 5.05–4.94 (m, 2H), 4.70 (s, 1H), 4.07 (t, 2H, $J = 6.6$ Hz), 3.82–3.77 (m, 2H), 3.72–3.55 (m, 2H), 2.32 (t, 2H, $J = 7.3$ Hz), 2.10–2.04 (m, 3H), 1.88–1.78 (m, 1H), 1.68–1.61 (m, 4H), 1.52–1.42 (m, 6H), 1.28 (d, 3H, $J = 6.1$ Hz), 1.13 (d, 3H, $J = 6.1$ Hz). ^{13}C NMR (63 MHz, $CDCl_3$); δ 174.1, 138.5, 115.0, 96.0, 77.4, 75.3, 71.1, 70.0, 69.5, 68.3, 64.5, 36.9, 35.4, 34.4, 33.4, 28.2, 25.3, 25.1, 19.0, 17.8; IR (film) ν_{max}; 3422, 2926, 1730, 1439, 1374, 1240, 1124, 1094, 1042, 978, 908, 779 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{19}H_{34}O_6$ $[M+H]^+$ m/z, 359.2434; found, 359.2435.

*4.2.6. (6R)-(3-Phenoxybenzyl heptanoate)-3-deoxy-α-L-rhamnopyranoside (**3b**)*

A colorless oil; yield, 30%; $R_f = 0.40$ (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D^{20} = +65.0$ ($c = 0.1$, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$); δ 7.37–7.28 (m, 3H), 7.14–6.92 (m, 6H), 5.08 (s, 2H), 4.69 (s, 1H), 3.79–3.70 (m, 2H), 3.68–3.51 (m, 2H), 2.37 (t, 2H, $J = 7.3$ Hz), 2.08–2.03 (m, 3H), 1.87–1.76 (m, 1H), 1.72–1.61 (m, 2H), 1.55–1.40 (m, 4H), 1.26 (d, 3H, $J = 5.9$ Hz), 1.11 (d, 3H, $J = 6.1$ Hz); ^{13}C NMR (63 MHz, MeOD); δ 173.7, 157.6, 157.0, 138.1, 130.0, 129.9, 123.6, 122.7, 119.1, 118.4, 118.3, 95.9, 71.0, 70.1, 69.3, 68.0, 65.8, 36.8, 35.3, 34.3, 25.3, 24.9, 19.0, 17.8; IR (film) ν_{max}; 3457, 2927, 2851, 1737, 1579, 1487, 1444, 1380, 1256, 1211, 1159, 1118, 1043, 1026, 983, 692, 604, 493 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{26}H_{34}O_7$ $[M+H]^+$ m/z, 459.2383; found, 459.2381.

*4.2.7. (2R)-7-Octenyl-2,4-O-benzoyl-3-deoxy-α-L-rhamnopyranosyl-(1 → 2)-4-O-tert-butyl dimethyl silyl-3-deoxy-α-L-rhamnopyranoside (**6a**)*

A suspension of trichloroacetimidate glycosyl donor **4** (337 mg, 0.672 mmol), glycosyl acceptor **5c** (167 mg 0.448 mmol), and 4 Å molecular sieves (1.5 g) in dry CH_2Cl_2 (20 mL) was stirred at room temperature for 30 min. After cooling to −20 °C, $BF_3 \cdot OEt$ (0.17 mL) in dry CH_2Cl_2 (10 mL) was slowly added drop wise. The resulting mixture was stirred for 3 h. Saturated aqueous $NaHCO_3$ (20 mL) was added to quench the reaction. The molecular sieves were filtered through a Celite pad, and the filtrate was washed with brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel flash chromatography (EtOAc/hexane, 1:6) to provide compound **6a** (299 mg, 94%) as a colorless oil. $R_f = 0.39$ (hexane/EtOAc, 6:1); $[\alpha]_D^{20} = -37.1$ ($c = 0.52$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$); δ 8.12 (d, 2H, $J = 7.3$ Hz), 8.05 (d, 2H, $J = 7.3$ Hz), 7.62–7.57 (m, 2H), 7.50–7.44 (m, 4H), 5.83–5.80 (m, 1H), 5.22 (m, 2H), 5.05–4.93 (m, 3H, C-1′), 4.87 (s, 1H, C-1), 4.18-4.14 (m, 1H), 3.83 (br s, 2H), 3.70–3.62 (m, 2H), 2.47–2.41 (m, 1H), 2.33–2.22 (m, 1H), 2.09–2.04 (m, 3H), 1.88–1.79 (m, 1H), 1.60–1.56 (m, 1H), 1.43 (br s, 5H), 1.26 (m, 6H) 1.15 (d, 3H, $J = 6.0$ Hz), 0.09 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$); δ 165.8, 139.0, 133.4, 130.0, 129.9, 129.8, 128.6, 114.5, 95.5, 95.0, 76.0, 71.5, 71.0, 70.6, 70.2, 68.8, 67.3, 37.2, 33.9, 29.8, 28.9, 25.4, 19.2, 18.3, 18.1, 18.0, −4.0, −4.6; IR (film) ν_{max}; 3066, 2938, 2856, 1719, 1596, 1456, 1386, 1316, 1269, 1159, 1100, 1071, 1024, 884, 832, 779, 715 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{40}H_{58}O_9Si$ $[M+H]^+$ m/z, 711.3928; found, 711.3927.

*4.3. General procedure for the deprotection of benzoyl groups (**5b**, **6b**, and **12b**)*

A suspension of protected glycolipids was dissolved in dry MeOH. After cooling to 0 °C, freshly prepared NaOMe was added. The resulting mixture was stirred for 8 h, and an acidic ion exchange resin (Amberlite IR-120) was added for neutralization. The mixture was stirred for a few minutes and after neutralization (monitored using pH paper) the resin was filtered off, washed with methanol, and the filtrate was concentrated under vacuum. The residue was purified by silica gel flash chromatography (hexane/EtOAc) to

provide the pure glycolipid derivative. (See Supplementary materials for the spectral data).

4.4. Preparation of compounds **8b** and **9b** via **8a** and **9a**

To a stirred solution of compound **7a** (87 mg, 0.15 mmol) or compound **7b** (106 mg, 0.18 mmol) in anhydrous toluene (40 mL), Grubbs' second-generation catalyst [((Mes)$_2$Im)(Cy$_3$P)Cl$_2$Ru = CHPh] [17] (12 mg) was added in dry toluene, and the solution was heated to reflux for 20 h. The mixture was then evaporated under reduced pressure, and Grubbs' catalyst was removed using a silica filter. Next, the reaction mixture was dissolved in dry ethanol (10 mL) and treated with 10% Pd/C (10 mg) under a H_2 atmosphere (1 atm) at 0 °C for 2 h. The suspension was then filtered through a Celite pad, and the filtrate was concentrated under vacuum. The residue was purified by silica gel flash chromatography (EtOAc/hexane, 1:3) to provide compounds **8a** (17 mg, 21%) and **9a** (15 mg, 15%) as a colorless oil. Deprotection of the TBDMS group was achieved by addition of intermediates of compound **8a** (17 mg, 0.03 mmol) or **9a** (15 mg, 0.03 mmol) in dry pyridine (1 mL) to a solution of the residue in HF/pyridine (5.5 μl, 0.03 mol). After 24 h, the resulting mixture was extracted with EtOAc (3 × 10 mL) and washed with 1 N HCl (3 × 10 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (2 × 10 mL) prior to drying over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by silica gel flash chromatography (EtOAc/hexane, 2:1) to give compound **8b** (10 mg, 15%) or **9b** (9 mg, 12%) as colorless oils.

4.4.1. (11R)-(Undecanoic acid)-3-deoxy-α-L-rhamnopyranosyl-(1 → 2)-3-deoxy-α-L-rhamnopyranoside-(1,2-lactone) (**8b**)

R_f = 0.31 (hexane/EtOAc, 1:1); $[\alpha]_D^{20} = -30.9$ (c = 0.53, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$); δ 5.20 (s, 1H), 4.91 (s, 1H), 4.66 (s, 1H), 3.83–3.77 (m, 2H), 3.70–3.65 (m, 2H), 3.63–3.52 (m, 2H), 2.34–2.30 (m, 2H), 2.03 (br s, 2H), 1.97–1.82 (m, 2H), 1.70–1.60 (m, 2H), 1.28–1.22 (m, 21H); ^{13}C NMR (63 MHz, $CDCl_3$); δ 174.1, 97.6, 92.0, 79.1, 72.9, 70.7, 69.9, 69.0, 68.3, 35.0, 34.6, 34.3, 32.1, 29.8, 29.5, 29.3, 28.7, 28.2, 25.5, 25.1, 20.8, 18.0; IR (film) ν_{max}; 3417, 2926, 2856, 1736, 1456, 1374, 1246, 1141, 1094, 1048, 1018, 983, 750 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{23}H_{40}O_8$ $[M+H]^+$ m/z, 445.2801; found, 445.2793.

4.4.2. (11S)-(Undecanoic acid)-3-deoxy-α-L-rhamnopyranosyl-(1 → 4)-3-deoxy-α-L-rhamnopyranoside-(1,4-lactone) (**9b**)

R_f = 0.46 (hexane/EtOAc, 1:2); $[\alpha]_D^{20} = -48.6$ (c = 0.35, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$); δ 4.89–4.84 (m, 1H), 4.78 (d, 2H, J = 2.3 Hz), 3.90–3.86 (m, 5H), 3.67–3.58 (m, 1H), 2.35–2.33 (m, 2H), 2.04–1.99 (m, 2H), 1.93–1.89 (m, 2H), 1.65 (br s, 2H), 1.29–1.20 (m, 21H); ^{13}C NMR (63 MHz, $CDCl_3$); δ 174.1, 94.8, 94.6, 73.2, 71.7, 69.7, 69.1, 67.9, 67.6, 34.9, 34.3, 31.5, 31.0, 28.7, 28.4, 27.6, 24.8, 24.6, 20.4, 18.0, 17.6; IR (film) ν_{max}; 3437, 2925, 2854, 1738, 1462, 1377, 1247, 1152, 1133, 1112, 1034, 757 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{23}H_{40}O_8$ $[M+H]^+$ m/z, 445.2801; found, 445.2800.

4.4.3. (2R)-(n-Octane-2-yl)-2,4-di-O-pentanoyl-3-deoxy-α-L-rhamnopyranosyl-(1 → 2)-3-deoxy-α-L-rhamnopyranoside (**10b**) via (**10a**)

Compound **7c** (43 mg, 0.06 mmol) was dissolved in dry EtOAc (2 mL) and treated with 10% Pd/C (10 mg) under H_2 atmosphere (1 atm) at 0 °C for 5 h with stirring. The suspension was filtered through a Celite pad, and the filtrated was concentrated. The residue was purified by silica gel flash chromatography (EtOAc/hexane, 1:3) to provide intermediate **10a** (40 mg) as a colorless oil. For deprotection of the TBDMS group, HF/pyridine (10.1 μl, 0.06 mmol) was added to a solution of the intermediate **10a** (40 mg, 0.06 mmol) dissolved in anhydrous pyridine (1 mL). After 24 h of stirring, the resulting mixture was extracted with EtOAc (3 × 10 mL) and washed with 1 N HCl (3 × 10 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (2 × 10 mL) prior to drying over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by silica gel flash chromatography (EtOAc/hexane, 1:2) to provide compound **10b** (26 mg, 78%) as a colorless oil. R_f = 0.65 (hexane/EtOAc, 2:1); $[\alpha]_D^{20} = -30.9$ (c = 0.27, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$); δ 4.88 (s, 1H), 4.79 (br s, 2H), 4.74 (s, 1H), 3.93–3.84 (m, 1H), 3.76 (br s, 2H), 3.71–3.51 (m, 2H), 2.36–2.28 (m, 4H), 2.05–2.00 (m, 3H), 1.76–1.64 (m, 1H), 1.61–1.50 (m, 4H), 1.39–1.24 (m, 14H), 1.15–1.09 (m, 9H), 0.93–0.87 (m, 9H); ^{13}C NMR (63 MHz, $CDCl_3$); δ 173.4, 173.0, 95.3, 94.8, 75.1, 71.6, 70.2, 69.8, 69.6, 68.2, 67.1, 37.3, 34.3, 34.1, 32.5, 31.9, 29.8, 29.4, 27.1, 27.0, 25.8, 22.8, 22.3, 19.1, 17.8, 14.2, 13.8; IR (film) ν_{max}; 3518, 2960, 2931, 2857, 1743, 1463, 1378, 1248, 1173, 1154, 1109, 1032, 986 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{30}H_{54}O_9Na$ $[M+Na]^+$ m/z, 581.3666; found, 581.3669.

4.4.4. (12R)-Methyl octadecanoate-2,4-di-O-benzoyl-3-deoxy-α-L-rhamnopyranoside (**12a**)

A suspension of trichloroacetimidate glycosyl donor **4** (498 mg, 0.99 mmol) and glycosyl acceptor **11** (311 mg 0.99 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 30 min. After cooling to −78 °C, 1 M $SnCl_4$ (0.5 mL, 0.50 mmol) was slowly added drop wise. The resulting mixture was then stirred for 5 h, after which saturated aqueous $NaHCO_3$ (10 mL) was then added to quench the reaction, followed by extraction with EtOAc (3 × 20 mL). The filtrate was washed with brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel flash chromatography (EtOAc/hexane, 1:2) to provide **12a** (479 mg, 74%) as a colorless oil. R_f = 0.49 (hexane/EtOAc, 2:1); $[\alpha]_D^{20} = +37.6$ (c = 0.50, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$); 8.13–8.03 (m, 4H), 7.62–7.56 (m, 2H), 7.50–7.43 (m, 4H), 5.24–5.14 (m, 2H), 4.93 (s, 1H), 4.20–4.13 (m, 1H), 3.66 (br s, 4H), 2.45–2.40 (m, 1H), 2.29 (t, 2H, J = 7.5 Hz), 2.23–2.16 (m, 1H), 1.60–1.52 (m, 6H), 1.30 (br s, 25H), 0.89–0.86 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$); δ 174.3, 165.9, 165.8, 133.3, 130.2, 130.0, 129.7, 128.6, 95.4, 78.5, 77.4, 71.2, 70.8, 67.1, 51.5, 34.7, 34.2, 33.5, 31.9, 29.8, 29.7, 29.6, 29.4, 29.3, 25.7, 25.1, 25.0, 22.8, 18.0, 14.2; IR (film) ν_{max}; 2926, 2854, 1725, 1452, 1265, 1108, 1069, 1027, 711 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{39}H_{56}O_8Na$ $[M+Na]^+$ m/z, 675.3873; found, 675.3870.

4.4.5. (12R)-Octadecanoic acid-3-deoxy-α-L-rhamnopyranosyl-(1 → 4)-3-deoxy-α-L-rhamnopyranoside (**14**)

Debenzoylation of compound **13a** was followed by the general procedure of deprotection to obtain deprotected glycolipid (94 mg, 54%). Next, the deprotected glycolipid (94 mg, 0.16 mmol) was dissolved in THF–H_2O 1:1 (2 mL). To this solution 10% NaOH (0.1 mL) was slowly added drop wise and stirred for 4 h. After 4 h, the mixture was diluted by EtOAc (2 mL) and was stirred with 10% HCl (2 mL) for 1 h. The organic layers were evaporated under vacuum. The residue was purified by silica gel flash chromatography (CH_2Cl_2/MeOH, 7:1) to provide pure compound **14** (47 mg, 51%) as a colorless oil. R_f = 0.33 (CH_2Cl_2/MeOH, 7:1); $[\alpha]_D^{20} = -55.1$ (c = 0.51, $CHCl_3$); ^{1}H NMR (250 MHz, MeOD); δ 4.78 (s, 1H), 4.65 (s, 1H), 3.78–3.77 (m, 2H), 3.65–3.60 (m, 5H), 2.28–2.26 (t, 2H, J = 7.3 Hz), 2.04–1.99 (m, 2H), 1.98–1.60 (m, 2H), 1.59–1.50 (m, 6H), 1.32 (s, 22H), 1.26–1.20 (m, 6H), 0.91–0.89 (m, 3H); ^{13}C NMR (63 MHz, MeOD); δ 178.1, 99.5, 98.0, 78.5, 75.7, 71.3, 71.2, 69.6, 68.6, 68.2, 35.8, 35.1, 34.6, 33.2, 33.0, 30.8, 30.7, 30.6, 30.4, 30.2, 26.7, 26.1, 26.0, 23.7, 18.2, 18.1, 18.0, 14.4; IR (film) ν_{max}; 3393, 2926, 2856, 1666, 1456, 1334, 1258, 1100, 1042, 978, 832, 674 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{30}H_{56}O_9Na$ $[M+Na]^+$ m/z, 583.3822; found, 583.3822.

*4.4.6. (12R)-(Methyloctadecanoate)-3-deoxy-α-L-rhamnopyranosyl-(1 → 2)-3-deoxy-α-L-rhamnopyranosyl-(1 → 4)-3-deoxy-α-L-rhamnopyranoside (**15**)*

A suspension of trichloroacetimidate glycosyl donor **4** (190 mg, 0.38 mmol), glycosyl acceptor **12b** (169 mg 0.38 mmol), and 4 Å molecular sieves (1.0 g) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 30 min. After cooling to −78 °C, $BF_3{\cdot}OEt$ (24 μl, 0.19 mmol) was slowly added drop wise. The resulting mixture was stirred for 3 h. Saturated aqueous $NaHCO_3$ (20 mL) was then added to quench the reaction. The molecular sieves were filtered through a Celite pad, and the filtrate was washed with brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel flash chromatography (EtOAc/hexane, 1:2) to give compounds **13a** (235 mg, 79%) and **13b** (94 mg, 7%) as colorless oils, respectively. Debenzoylation of compound **13b** by the general procedure described above gave compound **15** (38 mg, 64%) as a colorless oil. $R_f = 0.48$ (CH_2Cl_2/MeOH, 7:1); $[\alpha]_D^{20} = -83.1$ ($c = 0.51$, $CHCl_3$); ^{1}H NMR (250 MHz, MeOD); δ 4.81 (s, 1H), 4.66 (m, 2H), 3.79 (br s, 3H), 3.72 (br s, 1H), 3.64 (s, 3H), 3.62–3.53 (m, 6H), 2.31 (t, 2H, $J = 7.2$ Hz), 2.03–1.94 (m, 3H), 1.85–1.73 (m, 3H), 1.65–1.51 (m, 6H), 1.31 (s, 22H), 1.25–1.20 (m, 9H), 0.90–0.88 (m, 3H); ^{13}C NMR (63 MHz, MeOD); δ 176.0, 99.6, 98.1, 96.0, 78.6, 75.2, 71.8, 71.5, 71.4, 71.3, 69.7, 69.6, 69.3, 68.2, 68.1, 35.9, 34.8, 34.6, 33.0, 30.7, 30.4, 30.2, 29.1, 26.7, 26.0, 23.7, 18.8, 18.2, 18.1, 14.5; IR (film) ν_{max}; 3418, 2929, 2855, 1741, 1454, 1370, 1251, 1205, 1128, 1105, 1037, 982, 855, 836 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{37}H_{68}O_{12}Na$ $[M + Na]^+$ *m/z*, 727.4608; found, 727.4603.

*4.4.7. (2R)-7-Octenyl-2,4-di-O-benzoyl-3-deoxy-α-L-rhamnopyranosyl-(1 → 2)-2,4-di-O-benzoyl-3-deoxy-α-L-rhamnopyranosyl-(1 → 4)-3-deoxy-α-L-rhamnopyranoside (**16**)*

A suspension of glycosyl donor **4** (1.08 g, 2.16 mmol), glycosyl acceptor **5b** (279 mg, 1.08 mmol), and 4 Å molecular sieves (2 g) in dry CH_2Cl_2 (20 mL) was stirred at room temperature for 30 min. After cooling to −20 °C, TMSOTf (0.1 mL, 0.54 mmol) was added. The resulting mixture was then stirred for 5 h and afterwards was diluted with CH_2Cl_2 (10 mL). The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL). The molecular sieves were filtered through a Celite pad. The filtrate was washed with brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel flash chromatography (EtOAc/hexane, 1:6) to provide compound **16** (858 mg, 85%) as a colorless oil. $R_f = 0.2$ (hexane/EtOAc, 6:1); $[\alpha]_D^{20} = -36.5$ ($c = 12.33$, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$); δ 8.14–8.10 (m, 2H), 8.08–7.99 (m, 6H), 7.62–7.54 (m, 4H), 7.49–7.40 (m, 8H), 5.93–5.76 (m, 1H), 5.30–5.15 (m, 4H), 5.06 (br s, 2H), 5.00–4.99 (m, 2H), 4.94 (s, 1H), 4.24–4.08 (m, 2H), 3.95–3.72 (m, 4H), 2.45–2.39 (m, 2H), 2.33–2.19 (m, 2H), 2.14–2.09 (m, 2H), 1.92–1.72 (m, 2H), 1.65–1.47 (m, 6H), 1.42 (d, 3H, $J = 6.0$ Hz), 1.33 (d, 3H, $J = 6.2$ Hz), 1.30 (d, 3H, $J = 6.2$ Hz), 1.17 (d, 3H, $J = 6.0$ Hz); ^{13}C NMR (63 MHz, $CDCl_3$); δ 179.2, 165.8, 165.7, 139.0, 133.3, 130.0, 129.9, 129.7, 128.5, 114.5, 96.0, 94.9, 93.0, 75.5, 72.4, 71.7, 71.0, 70.9, 70.5, 67.8, 67.5, 67.4, 37.0, 33.8, 29.7, 29.6, 28.9, 25.3, 19.1, 18.6, 17.9, 14.3; IR (film) ν_{max}; 3248, 1723, 1625, 1401, 1266, 1098, 1053, 1029, 767, 706 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{54}H_{62}O_{14}Na$ $[M + Na]^+$ *m/z*, 957.4037; found, 957.4031.

*4.4.8. (2R)-[(6-Oxiran-2-yl)hexan-2-yloxy]-3-deoxy-α-L-rhamnopyranosyl-(1 → 4)-3-deoxy-α-L-rhamnopyranosyl-(1 → 2)-3-deoxy-α-L-rhamnopyranoside (**17**)*

Debenzoylation of protected compound **16** (94 mg, 0.10 mmol) by the general procedure gave the deprotected glycolipid (48 mg, 94%) as a colorless oil. The debenzoylated glycolipid (48 mg, 0.10 mmol) and *m*-CPBA (32 mg, 0.20 mmol) were then dissolved in dry CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was then stirred for 24 h and quenched by addition of saturated $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and was washed with saturated $NaHCO_3$ (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give crude product, which was subsequently purified on a silica gel column (CH_2Cl_2/MeOH, 7:1) to give compound **17** (25 mg, 50%) as a colorless oil. $R_f = 0.30$ (CH_2Cl_2/MeOH, 7:1); $[\alpha]_D^{20} = -108.6$ ($c = 0.14$, $CHCl_3$); ^{1}H NMR (250 MHz, MeOD); δ 4.81 (s, 1H), 4.66 (s, 1H), 4.65 (s, 1H), 3.80–3.71 (m, 5H), 3.58–3.47 (m, 5H), 2.92 (br s, 1H), 2.75–2.72 (t, 1H, $J = 4.9$ Hz), 2.49–2.46 (m, 1H), 2.27–2.22 (m, 1H), 2.03–1.93 (m, 2H), 1.84–1.65 (m, 3H), 1.63–1.57 (m, 2H), 1.51 (m, 6H), 1.26–1.20 (m, 9H), 1.13 (d, 3H, $J = 6.0$ Hz); ^{13}C NMR (100 MHz, MeOD) δ 97.5, 94.0, 93.8, 73.3, 70.3, 69.6, 69.1, 69.0, 67.4, 67.3, 66.9, 65.9, 65.8, 51.0, 45.4, 35.9, 33.6, 31.2, 26.9, 24.6, 24.4, 17.0, 16.5, 15.7; IR (film) ν_{max}; 3413, 2924, 2360, 1731, 1383, 1245, 1124, 1034, 981, 668 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{26}H_{46}O_{11}$ $[M + H]^+$ *m/z*, 535.3118; found, 535.3124.

*4.4.9. Preparation of (2R)-(8-azidooctanyl)-3-deoxy-α-L-rhamnopyranosyl-(1 → 4)-3-deoxy-α-L-rhamnopyranosyl-(1 → 2)-3-deoxy-α-L-rhamnopyranoside (**20**)*

Under a nitrogen atmosphere, compound **18** (58 mg, 0.06 mmol) in dry CH_2Cl_2 (2 mL) was added with Et_3N (10 mL, 0.07 mmol) and stirred for 10 min at 0 °C followed by addition of *p*-toluenesulfonic chloride (18 mg, 0.10 mmol). The reaction mixture was then stirred for 4 h and quenched with H_2O. The mixture was extracted with EtOAc (3 × 20 mL) and washed with brine (2 × 20 mL). The extract was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by a silica gel column (EtOAc/hexane, 1:4) to provide tosylated glycolipid (50 mg, 72%) as colorless oil. Next, a solution of tosylated glycolipid (50 mg, 0.05 mmol) in DMF (2 mL) was stirred at room temperature with sodium azide (5.8 mg, 0.10 mmol) for 8 h. The mixture was poured onto water (10 mL), extracted with EtOAc (3 × 20 mL), and washed with brine (2 × 20 mL). After the mixture was concentrated under vacuum, the residue was purified by silica gel flash chromatography (EtOAc/hexane, 1:7) to obtain azide glycolipid (40 mg, 90%) as colorless oil. Finally, debenzoylation of the azide glycolipid (40 mg, 0.05 mmol) by the general procedure afforded compound **20** (22 mg, 96%) as a colorless oil. $R_f = 0.25$ (CH_2Cl_2/MeOH, 10:1); $[\alpha]_D^{20} = -136.9$ ($c = 0.79$, $CDCl_3$); ^{1}H NMR (400 MHz, MeOD); δ 4.86 (s, 1H), 4.67 (s, 1H), 4.65 (s, 1H), 3.80–3.72 (m, 5H), 3.66–3.49 (m, 4H), 3.34–3.31 (m, 1H), 2.28–2.21 (m, 1H), 2.08–1.94 (m, 3H), 1.84–1.70 (m, 2H), 1.67–1.62 (m, 1H), 1.60–1.56 (m, 2H), 1.53–1.49 (m, 2H), 1.40–1.38 (m, 5H), 1.29 (s, 2H), 1.25–1.20 (m, 9H), 1.13 (d, 3H $J = 6.0$ Hz); ^{13}C NMR (100 MHz, MeOD); δ 99.8, 96.3, 96.0, 75.7, 72.7, 71.9, 71.5, 71.3, 69.7, 69.6, 69.2, 68.2, 68.1, 53.9, 38.1, 35.9, 30.2, 29.9, 29.2, 27.8, 26.8, 19.4, 18.8, 18.1; IR (film) ν_{max}; 3319, 2931, 2857, 2095, 1735, 1654, 1455, 1374, 1248, 1128, 1037, 983 cm^{-1}; HRMS calcd for $C_{26}H_{47}N_3O_{10}$ $[M]^+$ *m/z*, 561.3261; found, 561.3244.

*4.4.10. (6R)-(Methylheptanoate)-3-deoxy-α-L-rhamnopyranosyl-(1 → 4)-3-deoxy-α-L-rhamnopyranosyl-(1 → 2)-3-deoxy-α-L-rhamnopyranoside (**21**)*

A suspension of compound **19** (53 mg, 0.10 mmol) and *p*-TsOH (2 mg, 0.01 mmol) in dry MeOH (3 mL) was stirred for 14 h at 0 °C. The mixture was quenched by H_2O (10 mL), extracted with EtOAc (3 × 20 mL), and washed with brine (2 × 20 mL). The organic layer was separated and dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by silica gel flash chromatography (CH_2Cl_2/MeOH, 7:1) to afford compound **21** (26 mg, 47%) as colorless oil. $R_f = 0.20$ (CH_2Cl_2/MeOH, 7:1); $[\alpha]_D^{20} = -138.9$ ($c = 0.80$, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD); δ 4.85 (s, 1H), 4.67 (s, 1H), 4.65 (s, 1H), 3.80–3.71 (m, 5H), 3.65 (s, 3H), 3.64–3.48 (m, 5H), 2.34 (t,

2H, $J = 7.6$ Hz), 2.26–2.23 (m, 1H), 2.04–1.94 (m, 2H), 1.93–1.68 (m, 3H), 1.65–1.61 (m, 2H), 1.59–1.39 (m, 4H), 1.25–1.20 (m, 9H), 1.13 (d, 3H, $J = 6.0$ Hz); ^{13}C NMR (100 MHz, MeOD); δ 175.8, 99.8, 96.4, 96.0, 75.7, 72.6, 71.9, 71.5, 71.3, 69.7, 69.6, 69.3, 68.2, 68.1, 52.0, 37.9, 35.9, 34.8, 29.2, 26.4, 25.9, 19.4, 18.8, 18.1; IR (film) ν_{max}; 3427, 1733, 1653, 1375, 1038, 983 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{26}H_{46}O_{12}Na$ $[M + Na]^+$ m/z, 573.2887; found, 573.2895.

4.5. General procedure for the amide glycolipids (**22a**, **22b** and **22c**)

To a solution of acid glycolipid **19** (15 mg, 0.028 mmol) and DMAP (3.3 mg, 0.028 mmol) in DMF (2 mL), either furfurylamine (2.70 mg, 0.028 mmol), 3-bromoaniline (4.78 mg, 0.028 mmol) or 4-methylpiperidine (2.76 mg, 0.028 mmol), was added at room temperature. After stirring for 10 min, EDC (5.33 mg, 0.028 mmol) was added drop wise to the mixture. The reaction was stirred for 24 h, and concentrated under vacuum. Purification of this residue by silica gel flash chromatography (CH_2Cl_2/MeOH, 7/1–4/1) afforded compounds **22a** (8 mg, 47%), **22b** (10 mg, 76%) or **22c** (9.8 mg, 58%), respectively, all as colorless oils.

4.5.1. (6R)-(Furfurylheptanamide)-3-deoxy-α-L-rhamnopyranosyl-(1 → 4)-3-deoxy-α-L-rhamnopyranosyl-(1 → 2)-3-deoxy-α-L-rhamnopyranoside (**22a**)

$R_f = 0.53$ (CH_2Cl_2/MeOH, 7:1); $[\alpha]_D^{20} = -40.2$ ($c = 0.23$, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD); δ 7.41 (d, 1H, $J = 1.6$ Hz), 6.34–6.33 (dd, 1H, $J = 2.0, 1.6$ Hz), 6.23–6.22 (d, 1H, $J = 3.2$ Hz), 4.85 (s, 1H), 4.66 (s, 1H), 4.65 (s, 1H), 4.34 (s, 2H), 3.79–3.71 (m, 5H), 3.64–3.52 (m, 5H), 2.25 (m, 1H), 2.24–2.20 (t, 2H, $J = 7.2$ Hz), 1.95–1.94 (m, 2H), 1.84–1.69 (m, 3H), 1.65–1.62 (m, 2H), 1.55–1.37 (m, 4H), 1.24–1.20 (m, 9H), 1.12 (d, 3H, $J = 6.0$ Hz); ^{13}C NMR (100 MHz, MeOD); δ 176.0, 143.3, 111.4, 108.1, 99.8, 96.4, 96.1, 79.5, 75.7, 72.8, 71.9, 71.5, 71.4, 69.7, 69.3, 68.3, 68.2, 38.0, 37.1, 36.8, 35.9, 30.7, 29.2, 26.9, 26.4, 19.4, 18.9, 18.1; IR (film) ν_{max}; 3424, 2923, 2852, 1872, 1738, 1650, 1537, 1453, 1377, 1255, 1126, 1034, 981, 752 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{30}H_{49}NO_{12}$ $[M + H]^+$ m/z, 616.3333; found, 616.3330.

4.5.2. (6R)-(3-Bromoanilinylheptanamide)-3-deoxy-a-L-rhamnopyranosyl-(1 → 4)-3-deoxy-α-L-rhamnopyranosyl-(1 → 2)-3-deoxy-α-L-rhamnopyranoside (**22b**)

$R_f = 0.58$ (CH_2Cl_2/MeOH, 7:1); $[\alpha]_D^{20} = -25.8$ ($c = 0.24$, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD); δ 8.13 (s, 1H, NH), 7.89 (s, 1H), 7.46–7.45 (m, 1H), 7.22–7.20 (m, 2H), 4.85 (s, 1H), 4.65 (s, 1H), 4.64 (s, 1H), 3.79–3.69 (m, 5H), 3.65–3.52 (m, 5H), 2.39 (t, 2H, $J = 7.6$ Hz), 2.24–2.21 (m, 1H), 1.97–1.93 (m, 2H), 1.83–1.68 (m, 3H), 1.63–1.60 (m, 2H), 1.57–1.46 (m, 4H), 1.26–1.19 (m, 9H), 1.15–1.13 (d, 3H, $J = 6.0$ Hz); ^{13}C NMR (100 MHz, MeOD); δ 174.7, 141.5, 131.4, 127.8, 123.8, 123.3, 119.5, 99.8, 96.4, 96.0, 75.7, 72.8, 71.9, 71.5, 71.4, 69.7, 69.3, 68.3, 68.1, 38.1, 37.8, 35.9, 29.2, 26.7, 26.5, 19.4, 18.8, 18.1, 18.0; IR (film) ν_{max}; 3300, 2924, 2851, 2804, 1822, 1737, 1666, 1589, 1528, 1455, 1374, 1247, 1127, 1104, 1035, 983, 751 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{31}H_{48}BrNO_{11}Na$ $[M + Na]^+$ m/z, 712.2308; found, 712.2307.

4.5.3. (6R)-(4-Methylpiperidinyl heptanamide)-3-deoxy-α-L-rhamnopyranosyl-(1 → 4)-3-deoxy-α-L-rhamnopyranosyl-(1 → 2)-3-deoxy-α-L-rhamnopyranoside (**22c**)

$R_f = 0.61$ (CH_2Cl_2/MeOH, 4:1); $[\alpha]_D^{20} = -120.8$ ($c = 0.16$, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD) δ 4.86 (s, 1H), 4.67 (s, 1H), 4.65 (s, 1H), 4.50 (d, 1H, $J = 13.2$ Hz), 3.94 (d, 1H, $J = 12.8$ Hz), 3.80–3.71 (m, 5H), 3.66–3.52 (m, 5H), 3.08 (t, 1H, $J = 10.0$ Hz), 2.60 (t, 1H, $J = 12$ Hz), 2.40 (t, 2H, $J = 7.2$ Hz), 2.27–2.22 (m, 1H), 1.98–1.90 (m, 2H), 1.84–1.70 (m, 3H), 1.66–1.57 (m, 5H), 1.56–1.28 (m, 6H), 1.25–1.20 (m, 9H), 1.13 (d, 3H, $J = 6.4$ Hz), 0.96 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, MeOD); δ 171.5, 97.5, 94.1, 93.8, 73.4, 69.7, 69.2, 69.1, 67.5, 67.4, 67.0, 66.8, 66.0, 65.9, 45.2, 41.1, 33.7, 32.8, 31.8, 30.0, 29.4, 27.9, 26.9, 24.5, 24.3, 19.8, 17.1, 16.6, 15.8; IR (film) ν_{max}; 3364, 2955, 2924, 2849, 1726, 1620, 1451, 1384, 1123, 1040, 984 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{31}H_{55}NO_{11}$ $[M]^+$ m/z, 617.3775; found, 617.3705.

4.6. Measurement of anticancer activity

Human cancer cell lines of the lung (A549), ovary (SK-OV-3), brain (XF498), and the colon (HCT15), as well as melanoma cancer cells (SK-MEL-2), were used for *in vitro* cytotoxicity testing using the SRB (sulforhodamin B) assay [20]. The cells were maintained as stocks in RPMI 1640 (Gibco) supplemented with 10% fetal bovine serum (Gibco). Cell cultures were passaged once or twice weekly by using trypsin–EDTA to detach the cells from their culture flasks. The rapidly growing cells were harvested, counted, and incubated at the appropriate concentration ($1–2 \times 10^4$ cells/well) in 96-well plates. After incubation for 24 h, the compounds were dissolved in culture medium, applied to the culture wells in triplicate, and incubated for 48 h at 37 °C under a 5% CO_2/95% air atmosphere in a humidified incubator. The cultured cells were fixed with 10% cold TCA and stained with 0.4% SRB dissolved in 1% acetic acid. After solubilizing the bound stain with 10 mM unbuffered Trisma base solution (pH 10.5) using a gyratory shaker, the absorbance at 520 nm was measured spectrophotometrically in a microplate reader. Cytotoxic activity was evaluated by determining the concentration of compound that was required to inhibit protein synthesis by 50% (IC_{50}); activities were compared with that of doxorubicin in the same assay.

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Appendix. Supplementary data

General procedure and spectral data of compounds, **5b–c**, **6b**, **7a–c**, **8a**, **9a**, **10a**, **12b**, **13a–b**, **18**, **19**, and **20**. This material is available online at www.sciencedirect.com. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.ejmech.2009.03.007.

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Abbreviations

Bz: Benzoyl
SRB: sulforhodamin B
SAR: structure–anticancer activity relationship