Articles

Synthesis and Growth Inhibitory Properties of Glycosides of 1-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol, Analogs of the Antitumor Ether Lipid ET-18-OCH_3 (Edelfosine)

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Glycosylated antitumor ether lipids (GAELs), analogs of 1-*O*-octadecyl-2-*O*-methyl-*sn*-glycero-3-phosphocholine (**1**, ET-18-OCH_3, edelfosine), were synthesized in good overall yields by glycosylation of 1-*O*-alkyl-2-*O*-methyl-*sn*-glycerol and tested for *in vitro* antineoplastic activity against a variety of murine and human tumor cell lines. Stereospecific glycosylation was achieved by the use of 2-*O*-acetyl-3,4,6-tri-*O*-benzylglucopyranosyl and -mannopyranosyl trichloroacetimidates as donors, with trimethylsilyl trifluoromethanesulfonate as catalyst in the presence of molecular sieves at −78 °C. The GAELs differ from **1** in having the *sn*-3-phosphocholine residue replaced by one of the following monosaccharide residues: *β*- and α-2-deoxy-D-*arabino*-hexopyranosyl, α-D-mannopyranosyl, 2-*O*-methyl-*β*-D-glucopyranosyl, and 2-*O*-methyl-α-D-mannopyranosyl. 1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(2′-deoxy-*β*-D-*arabino*-hexopyranosyl)-*sn*-glycerol (**2**) was more effective than **1** in inhibiting the growth of MCF-7 (human breast cancer) and its adriamycin-resistant form MCF-7/adriamycin, and murine Lewis lung cancer cells. 2-Deoxy-*β*-D-*arabino*-hexopyranoside **2** was also an effective growth inhibitor of two drug-resistant leukemic cell lines, P388/Adr and L1210/vmdr.

Introduction

Edelfosine, 1-*O*-octadecyl-2-*O*-methyl-*sn*-glycero-3-phosphocholine (**1**), also known as ET-18-OCH_3, belongs to a family of antitumor ether lipids (AELs) that have been shown to specifically inhibit the growth of tumor cells, inhibit tumor cell invasion and metastasis, and enhance the tumoricidal capacity of macrophages (for recent reviews see refs 1, 2). Many AELs have been synthesized and analyzed for antitumor activity.[1,2] Some glycosylated antitumor ether lipids (GAELs) have been synthesized in which the 3-phosphocholine residue of **1** has been substituted by *O*-α- and *O*-*β*-D-glucosyl,[3] *O*-*β*-D-maltosyl,[4,5] *O*-*β*-D-lactosyl,[5] and *S*-α- and *S*-*β*-D-glucosyl.[3] The ET-16-OCH_3-*S*-*β*-D-glucoside[3] and ET-16-OCH_3-*O*-*β*-D-maltoside[6] were not cytotoxic to leukemic cells in vitro, whereas the other glycolipids displayed cytotoxic activities against epithelial[7] and mouse-derived[3] cancer cell lines that varied with cell type. In this report we present the synthesis of five new GAEL analogs of ET-16-OCH_3 (Figure 1), in which the phosphocholine residue has been replaced by 2-deoxy-*β*-D-*arabino*-hexopyranosyl (**2**) and 2-deoxy-α-D-*arabino*-hexopyranosyl (**3**), and by 2-*O*-alkyl-monosaccharides such as 2-*O*-methyl-*β*-D-glucopyranosyl (**4**) and 2-*O*-methyl-α-D-mannopyranosyl residues (**6**); in addition, α-D-mannopyranoside **5** was synthesized. These α- and *β*-D-GAELs, which differ from each other at the 2 position of the glycosyl residue, were prepared via the glycosylation of 1-*O*-hexadecyl-2-*O*-methyl-*sn*-glycerol (**7**) with glycosyl trichloroacetimidate donors **8** and **9**, followed by functionalization of the C-2′ position of the glycoside and deprotection. The present study also compares the in vitro growth inhibitory activities of these analogs against the following cells: A549 (human lung carcinoma), MCF-7 (human breast carcinoma) and its adriamycin-resistant form MCF-7/Adr, HT29 (human colon carcinoma), Lewis lung (murine lung carcinoma), P388 (murine leukemia) and its adriamycin-resistant form P388/Adr, L1210 (murine leukemia) and its vmdr form L1210/vmdr (transfected with a plasmid containing mdr 1).

Results and Discussion

I. Synthetic Chemistry. The synthesis of 1-*O*-hexadecyl-2-*O*-methyl-*sn*-glycerol (**7**) has been carried out previously starting from D-mannitol[4] and, although this approach affords **7** in moderate yields, it requires four laborious steps for the synthesis of the key intermediate, 3-*O*-benzyl-*sn*-glycerol. A more direct synthetic approach to **7** was reported[8] in which the Lewis acid-catalyzed (BF_3·Et_2O) regioselective ring opening of (*R*)-glycidyl arenesulfonates with 1-hexadecanol gives 1-*O*-hexadecyl-3-*O*-arenesulfonyl-*sn*-glycerol in moderate to good yield and high enantiomeric excess; alternatively, the *tert*-butyldiphenylsilyl ether of glycidol can be used as the precursor to **7**.[8] Whereas this procedure led to **7** after 2-*O*-methylation and 3-*O*-deprotection, the process is tedious to be scaled up. In the present work, we synthesized **7** (Scheme 1) by using an efficient and attractive method of synthesis of 3-*O*-protected-*sn*-glycerol developed on a small scale in this laboratory.[9,10] This procedure is based on asymmetric dihydroxylation[11] of allyl 4-methoxyphenyl ether using AD-mix-α in a mixture of 1:1 *tert*-butyl alcohol−water at 0 °C, to

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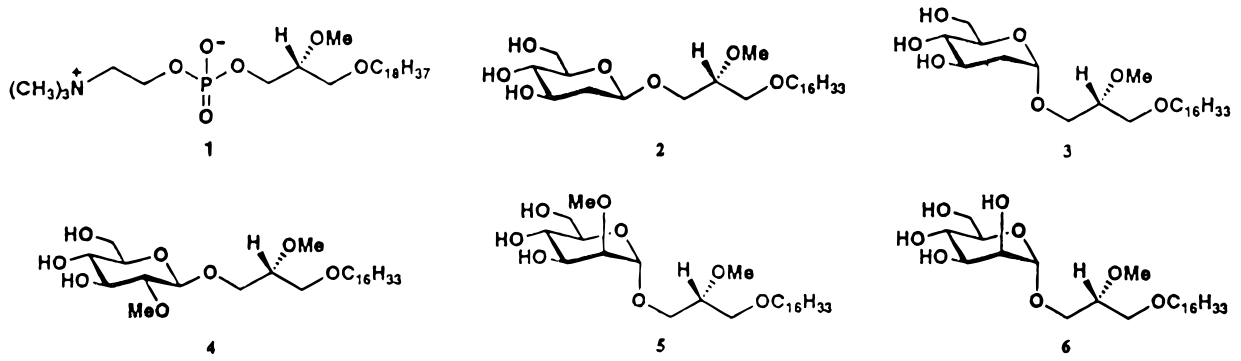
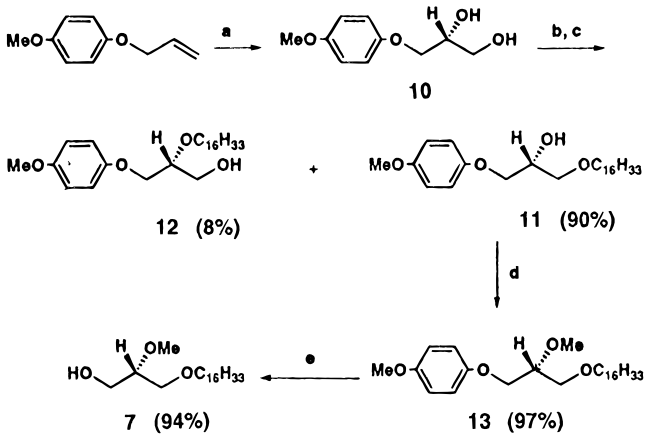


Figure 1. Structures of ET-18-OCH_3 (edelfosine, **1**) and the new GAELs (**2**−**6**).

Scheme 1.[a] Synthesis of **7** by Asymmetric Dihydroxylation

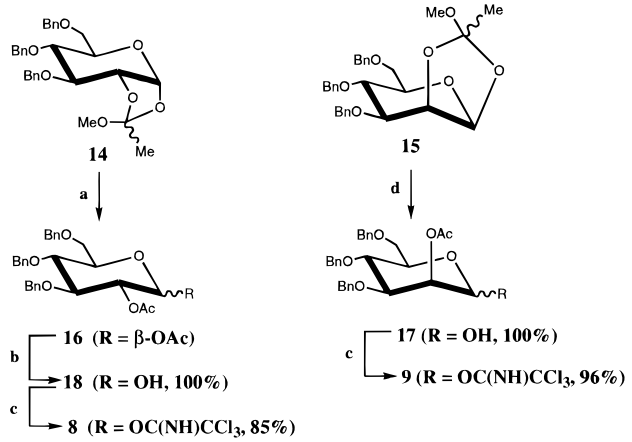


[a] Reagents: (a) AD-mix-α, 1:1 *tert*-BuOH/H_2O; (b) *n*-Bu_2SnO/MeOH; (c) *n*-$C_{16}H_{33}Br$, CsF, DMF; (d) MeI, NaH, DMF; (e) CAN, 4:1 MeCN−H_2O.

give 3-*O*-(4-methoxyphenyl)-*sn*-glycerol (**10**) in 90% chemical yield and 95% ee. Recrystallization of the purified 1,2-diol increased its enantiomeric excess. This procedure was recently modified in order to minimize the amounts of AD-mix-α employed for this reaction, as illustrated by enantioselective syntheses of **7** and *O*-benzyl-*sn*-glycerol.[10] Selective monoalkylation of **10** in DMF with 1-bromohexadecane via 1,2-*O*-stannylidene in the presence of cesium fluoride[10,12] afforded a mixture of monosubstituted glycerols, *sn*-1-*O*-hexadecyl (**11**), and *sn*-2-*O*-hexadecyl (**12**), in 97% overall yield. The ratio of **11**/**12** after chromatographic separation was 12:1. Confirmation for structures **11** and **12** was obtained by ^{13}C NMR spectroscopy. By INEPT experiments, the C-2 signal of the glycerol moiety was assigned; for **11**, the C-2 NMR signal appears at 69.53 ppm, whereas for **12** an expected downfield shift of the C-2 signal (78.69 ppm) was observed. After chromatographic separation of these two isomers, **11** was methylated (97%) by treatment with MeI−NaH−DMF, giving 1,2-di-*O*-alkyl-3-*O*-protected-*sn*-glycerol (**13**). Removal of the 3-*O*-(4-methoxyphenyl) function with ammonium cerium(IV) nitrate (CAN) in aqueous acetonitrile gave **7** in 95% yield after column purification.

The synthesis of 3-*O*-glyceryl acceptors via asymmetric dihydroxylation of allyl 4-methoxyphenyl ether (Scheme 1) is very simple, high yielding, and provides products with high enantiomeric excess. This procedure affords **7** in four steps and 74% overall yield, starting from the readily available allyl 4-methoxyphenyl ether. A practical advantage of this sequence is that this process can be scaled up to provide 20−30 g of **7** per reaction. At this level, the products of regioselective monoalkylation **11** and **12** can be separated readily by crystallization from hexane−ethyl acetate in excellent yields. Moreover, the ratio of **11**/**12** can be increased by using a mixture of methanol and chloroform (1:10 v/v) instead of pure methanol as the solvent for the *O*-stannylation of **10**.

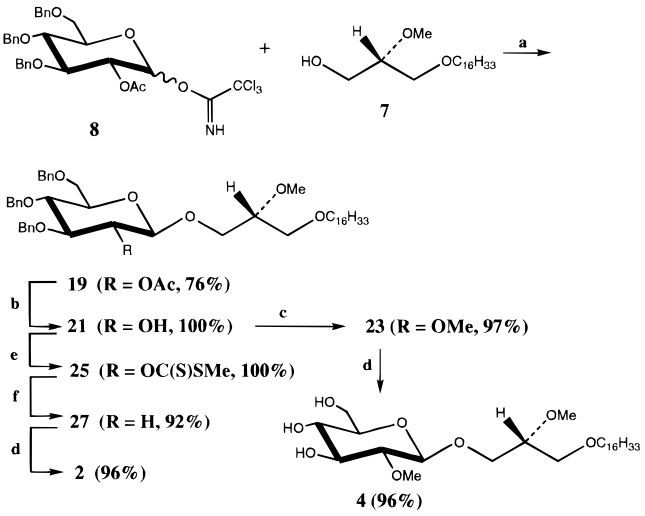
Scheme 2.[a] Synthesis of Glycosyl Donors **8** and **9**



[a] Reagents: (a) 100% AcOH; (b) H_2NNH_2·AcOH, DMF; (c) CCl_3CN, K_2CO_3, CH_2Cl_2; (d) 80% AcOH.

For the syntheses of glycoside analogs of **1**, with a 2-deoxy, 2-*O*-alkyl, or 2-axial-hydroxy function on the monosaccharide residue of the final product, the protecting groups of positions C-3, C-4, and C-6 of the glycosyl donor must enable preferential deprotection of the C-2 protecting group of the glycoside and also be resistant to the conditions used for 2-*O*-alkylation (in compounds **4** and **6**) and for deoxygenation via radical reduction of xanthates (in compounds **2** and **3**). For this purpose, a common synthon that suits both classes of compounds was selected. The use of trichloroacetimidates such as **8** and **9** matched this requirement.[13] 1,2-*trans*-Glycosyl donors with these characteristics, and an *O*-acetyl function at C-2 and *O*-benzyl functions at C-3, C-4, and C-6, are readily available from their respective benzylated 1,2-orthoesters (Scheme 2). For the synthesis of **8**, **14**[14] was acetolized in glacial acetic acid[15,16] to afford 1,2-*trans*-di-*O*-acetate **16**. The 1-*O*-acetate function was removed selectively by treatment of **16** with hydrazine acetate in DMF,[17] giving **18** quantitatively after aqueous workup. Hemiacetal **18** was treated with trichloroacetonitrile−potassium carbonate in dichloromethane to afford an α/β mixture of trichloroacetimidate **8** in 85% yield after flash chromatography. For the synthesis of **9**, the benzylated 1,2-

Scheme 3.[a] β-Glycosidation of Glycosyl Acceptor **7** by TMSOTf-Catalyzed Reaction with Glucosyl Donor **8** and Functionalization of the C-2′ Position



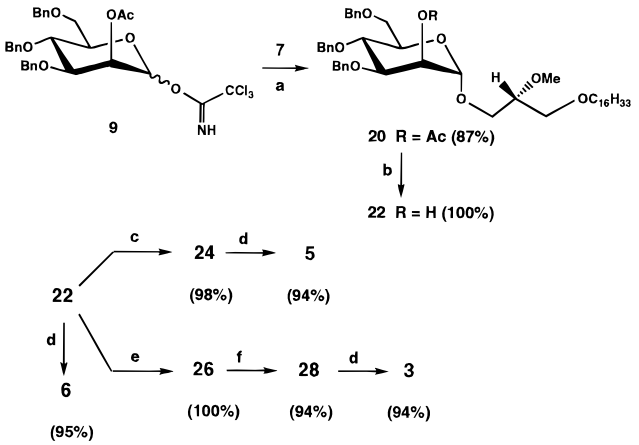
[a] Reagents: (a) TMSOTf, CH_2Cl_2, mol sieves (3 Å), −78 °C, 10 min; (b) NH_3, MeOH, rt, 15 min; (c) MeI, NaH, DMF; (d) H_2, Pd−C, 1:1 THF−AcOH; (e) CS_2, NaH, imidazole, MeI; (f) Bu_3SnH, AIBN, toluene.

orthoester **15**, which was prepared in a route analogous to that used to make **14**,[14] was hydrolyzed with 80% acetic acid at room temperature for 6 h; treatment of hemiacetal **17** with trichloroacetonitrile−potassium carbonate in dichloromethane gave **9** in high yield.

The use of 1,2-*trans*-di-*O*-acetyl derivatives in glycosylation reactions promoted by trimethylsilyl trifluoromethanesulfonate (TMSOTf) affords 1,2-*trans*-glycosides in high yields.[18,19] However, when **7** was glucosylated with 1,2-di-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranose **16** in dichloromethane, using a ratio of donor:acceptor:promoter of 1:1:1 at −20 °C, β-glycoside **19** was obtained in only 55% yield, along with 10% of the transesterification product of **7**. On the other hand, as shown in Scheme 3, glycosylation of **7** with **8** in dichloromethane promoted by TMSOTf catalysis at −78 °C (donor:acceptor:promoter, 1.1:1:0.035) in the presence of molecular sieves 3 Å proceeded in 10 min to give exclusively **19** in 76% yield. Similarly, glycosylation of **7** by using the 2-*O*-acetylmannosyl donor **9**, according to the same TMSOTf catalytic method described for the synthesis of **19**, led to the α-D-mannopyranoside **20** in 87% yield, without detection of any transesterification product (Scheme 4). Thus the stereochemistry of the 2′-*O*-acetyl group directs the outcome of the glycosidation reaction of imidates **8** and **9** with glycosyl acceptor **7**, independent of the composition of the anomeric mixture of the glycosyl donor. This result is consistent with recent reports of stereospecific glycosidation via neighboring-group participation in 2-*O*-acetylglycosyl trichloroacetimididates with TMSOTf as catalyst.[13,20]

The key feature of the next stage of this work was the functionalization of the C-2′ position of these two monosaccharides. The 2′-*O*-methyl group was introduced into **4** and **5** as follows (Scheme 3). First, the 2′-*O*-acetyl function of **19** and **20** was removed quantitatively by aminolysis using NH_3/MeOH, and then the 2′-hydroxy group was methylated by using MeI−NaH−DMF, to give **23** and **24** in 97% and 98% yields, respectively. The *O*-benzyl protecting groups were removed in 1:1 TMF−HOAc using Pd−C under a balloon pressure of hydrogen to afford the deblocked GAELs **4** and **5** in 96% and 94% yields, respectively.

Scheme 4.[a] α-Glycosidation of Glycosyl Acceptor **7** by TMSOTf-Catalyzed Reaction with Mannosyl Donor **9** and Functionalization of the C-2′ Position



[a] Reagents: (a) TMSOTf, CH_2Cl_2, mol sieves (3 Å), −78 °C, 10 min; (b) NH_3, MeOH, rt, 15 min; (c) MeI, NaH, DMF; (d) H_2, Pd−C, 1:1 THF−AcOH; (e) CS_2, NaH, imidazole, MeI; (f) Bu_3SnH, AIBN, toluene.

The 2′-deoxy function was introduced into **2** and **3** via radical reduction of xanthates (Schemes 3 and 4), which is a common procedure to deoxygenate carbinols.[21,22] The 2′-alcohols **21** and **22** were converted into their respective xanthates by treatment, in tetrahydrofuran, with sodium hydride, carbon disulfide, and a catalytic amount of imidazole followed by reaction with methyl iodide (Scheme 3). Xanthates **25** and **26** were radical-reduced with tributyltin hydride in the presence of α,α′-azobis(isobutyronitrile) (AIBN) in toluene to yield the protected 2′-deoxyglycosides **27** and **28** in yields of 92 and 94%, respectively. Similar yields have been reported for the preparation of 2-deoxyglycosides by the modified[23] Barton-type deoxygenation of secondary alcohols, in which a 2-*O*-(pentafluorophenoxy)thiocarbonyl intermediate is prepared.[24] The ^{13}C-NMR spectra of **27** and **28** showed an upfield shift of the C-2′ signal (36.68 and 35.42 ppm, respectively), which is characteristic of β- and α-2-deoxy-*arabino*-hexopyranosides. The ^{1}H-NMR spectrum of **27** showed the β H-1 anomeric signal at 4.46 ppm as a dd, and a ddd at 2.36 ppm, which was assigned to H-2′equatorial (H-2′e). The ^{1}H-NMR spectrum of **28** showed signals at 4.97 ppm (dd with very small coupling constants) and at 2.29 ppm (ddd), which were assigned to H-1′a and H-2′e, respectively. In each compound, the H-2′a signal was partially buried under a CH_2 triplet of the *sn*-1 *O*-*n*-alkyl chain between 1.4 and 1.8 ppm.

After careful purification of these β- and α-2-deoxy-*arabino*-hexopyranosides by column chromatography on silica gel, and elution with a gradient of polarity using hexane−ethyl acetate, we removed the *O*-benzyl protecting groups in 1:1 THF−HOAc in the presence of Pd−C and under a balloon pressure of hydrogen to give **2** and **3** in good yields after column purification. Finally, monosaccharides **2**−**5** were filtered through lipophilic Sephadex LH-20 using methanol to remove low molecular weight impurities.

II. Biological Results and Discussion. Table 1 presents the data for the *in vitro* biological evaluation of the growth inhibitory properties of GAELs **2**−**6** and

Table 1. Growth Inhibitory Properties of ET-18-OCH_3 (**1**) and GAELs **2**−**6**[a]

	GI_{50} (μM)					
cell line	**1**	**2**	**3**	**4**	**5**	**6**
A549	5.05 ± 0.80[b]	9.90 ± 0.99	19.65 ± 0.07	18.30 ± 0.14	15.55 ± 0.07	18.10 ± 0.14
MCF7	9.66 ± 2.50[b]	6.93 ± 0.12	24.45 ± 0.64	23.05 ± 0.64	18.20 ± 0.00	21.70 ± 0.57
MCF7/Adr	30.35 ± 5.07[b]	12.85 ± 0.85	24.40 ± 0.42	21.75 ± 0.63	18.55 ± 0.07	23.30 ± 0.71
HT29	2.20 ± 0.27[c]	7.59 ± 0.23	29.60 ± 0.28		20.00 ± 0.28	23.20 ± 0.85
Lewis lung	30.24 ± 6.32[d]	11.05 ± 0.49		26.00 ± 0.71		
P388	4.33 ± 1.37[e]	12.65 ± 0.78		18.10 ± 1.13		
P388/Adr	6.39 ± 2.43[e]	10.25 ± 2.34		29.30 ± 5.66		
L1210	3.32 ± 1.68[d]	7.02 ± 0.49	18.75 ± 0.49		15.45 ± 0.35	16.20 ± 0.99
L1210/vmdr	10.99 ± 6.36[d]	7.09 ± 0.33	26.95 ± 1.06		16.50 ± 1.13	18.90 ± 0.00

[a] Cells were treated with varying concentrations of drugs for 72 h. Details of the *in vitro* assay are described in the Experimental Section. GI_{50} values are the mean ±SD. The GI_{50} value from each experiment "*n*" was generated from three individual wells on two separate plates (six total wells); $n = 1$ for compounds **3**−**6**; $n = 2$ for most cell lines treated with compound **2**. [b] $n = 3$. [c] $n = 2$. [d] $n = 6$. [e] $n = 8$.

of edelfosine (**1**) on mouse and human tumor cells. The GI_{50} values (drug concentrations required to inhibit growth by 50%) indicate that 2′-deoxy-β-D-*arabino*-hexopyranoside **2** was more potent against every cell tested than its 2-*O*-methyl-2′-deoxy-β-D-*arabino*-hexopyranoside homolog **4**. The α anomers **3**, **5**, and **6** were less effective than **2** in inhibiting growth of the cell lines shown in Table 1. Compound **2** maintained high potency against the murine leukemia cell line L1210/vmdr, and against the drug-resistant tumor cell lines we investigated (MCF-7/Adr and P388/Adr). Compound **2** was highly effective against drug-sensitive MCF-7 (human breast cancer) cells, and was appreciably more effective than edelfosine (**1**) against mouse Lewis lung cells and the multidrug resistant human MCF7/Adr cell line. However, **1** had higher growth inhibitory activity than GAELs **2**−**6** against mouse leukemia P388 cells and P3888/adriamycin-resistant cells.

These biological results indicate that the deoxyglucopyranosyl analogs of **1** may be good candidates for further studies as new antitumor ether lipids, especially with regard to their activities against multidrug resistant cells. Although the use of glycosyl donors such as **8** and **9** led to 2′-deoxyglycosides in good overall yields (β-glycoside **2** in 36% yield; α-glycoside **3** in 55% yield in 11 steps starting from **10** and the corresponding benzylated orthoesters), this process involves a considerable number of steps that would be time consuming to scale up. More efficient routes to **2** and **3**, as well as new analogs of the GAELs family, need to be evaluated in future studies.

Conclusion

New glycosylated antimor ether lipids (GAELs) were synthesized by glycosylation of 1-*O*-hexadecyl-2-*O*-methyl-*sn*-glycerol (**7**), which was prepared from 3-*O*-(4-methoxyphenyl)-*sn*-glycerol (**10**) and analyzed for *in vitro* antitumor activity. 1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(2′-deoxy-β-D-*arabino*-hexopyranosyl)-*sn*-glycerol (**2**) was found to possess higher antitumor activity than its 2′-*O*-methyl-2′-deoxy-β-D-*arabino*-hexopyranoside analog **4** against a variety of murine and human tumor cell lines. Three α-glycosyl diglycerides (2′-deoxy-α-D-*arabino*-hexopyranoside **3**, α-D-mannopyranoside **6**, and 2-*O*-methyl-α-D-mannopyranoside **5**) had similar activities to **4** for all of the cell lines tested. The 2′-deoxy-β-D-*arabino*-hexopyranoside **2** was more effective than the prototypic AEL ET-18-OCH_3 (edelfosine, **1**) against MCF-7, MCF-7/Adr, Lewis lung, and L1210/vmdr cells.

Experimental Section

General Methods. The solvents used were dried and then distilled under a positive pressure of nitrogen as follows: dichloromethane was refluxed over calcium hydride and distilled before use; tetrahydrofuran (THF) was refluxed over sodium benzophenone ketyl and distilled before use; methanol was refluxed over $Mg(OMe)_2$ and distilled before use; toluene was distilled and then redistilled from calcium hydride before use. TMSOTf, CAN, cesium fluoride, dibutyltin oxide, 1-bromohexadecane, methyl iodide, tributyltin hydride, and AIBN were purchased from Aldrich. Anhydrous *N*,*N*-dimethylformamide (DMF), acquired from Janssen Chimica, was used without purification. Optical rotations were measured at 20 °C with a JASCO DIP-140 digital polarimeter in a cell of 1-dm pathlength; 1% solutions in chloroform were used unless otherwise stated. ^{1}H-NMR spectra were recorded with IBM-Bruker WP 200 and AMX-400 Bruker spectrometers at 200 and 400.13 MHz, respectively, for solutions in $CDCl_3$ (internal reference of Me_4Si). ^{13}C-NMR spectra were recorded with IBM-Bruker WP 200 and AMX-400 Bruker spectrometers at 75 and 100.57 MHz, respectively, and the ^{13}C chemical shifts are given by assigning 77.0 ppm for the central line of $CDCl_3$. Reactions were monitored using TLC aluminum plates of silica gel 60 F254 (EM Separations), and the spots were visualized by charring with 10% sulfuric acid in ethanol and/or short wavelength UV light. Column chromatography was carried out on silica gel 60 (230−400 mesh, purchased from Aldrich) isocratically unless otherwise stated, using a peristaltic pump. Solid synthons were dried under vacuum (0.02 mmHg), and all reactions were carried out under dry nitrogen using air-sensitive glassware (greaseless vacuum/gas manifold). Nitrogen gas was dried through a drying tower of granular anhydrous calcium chloride. Molecular sieves (3 Å) were dried at 150 °C under vacuum over P_2O_5 for 12 h and stored under vacuum over P_2O_5.

1-*O*-Hexadecyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (11) and 2-*O*-hexadecyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (12). A mixture of 3-*O*-(4-methoxyphenyl)-*sn*-glycerol (**10**, 0.737 g, 3.7 mmol), di-*n*-butyltin oxide (1.11 g, 4.46 mmol) in dry methanol (10 mL) was refluxed with stirring until the oxide was dissolved. The solvent was evaporated, and the solid was dried under vacuum for 3 h and then dissolved in DMF (30 mL). Cesium fluoride (1.5 g) and 1-bromohexadecane (1.57 mL, 5.13 mmol) were added. The mixture was stirred at room temperature until TLC (4:1 hexane−ethyl acetate) indicated that the reaction was complete. Ethyl acetate (20 mL) and water (0.5 mL) were added, and the mixture was stirred for 30 min. A white solid (dibutyltin oxide) was filtered, and the solvent was evaporated to give a crude mixture of **11** and **12**. The mixture of monoalkylated products was separated by column chromatography to afford **11** and **12**. Compound **11**: 1.42 g (90% yield). ^{1}H-NMR: δ 6.84−6.78 (m, 4H, Ph), 4.13 (m, 1H, H-2), 4.03−3.95 (m, 2H, H-3a, H-3b), 3.76 (s, 3H, OCH_3), 3.57 and 3.54 (dd, 2H, $J_{1a,1b} = 12.0$ Hz, $J_{1,2} = 4.0$ Hz, H-1a, H-1b), 3.46 (t, 2H, $J = 4.0$ Hz, OCH_2), 2.56 (1H, OH), 1.60 (t, 2H, $J = 6.0$ Hz, CH_2), 1.25 (s, 26H, CH_2), 0.88 (t, 3H, $J = 6.0$ Hz, CH_3). ^{13}C-NMR: δ 115.89, 114.99 (Ar), 72.02

(OCH_2), 71.97 (C-1), 70.16 (C-3), 69.53 (C-2), 56.02 (OCH_3). Compound **12**: 0.12 g (7.6% yield). ^{1}H-NMR: δ 6.87−6.80 (m, 4H, Ph), 3.89 (d, 2H, J = 4.4 Hz), 3.73−3.48 (m, 5H, H-1a, H-1b, H-2, H-3a, H-3b), 3.63 (s, OCH_3), 2.25 (1H, OH), 1.60 (t, 2H, J = 6.0 Hz, CH_2), 1.25 (s, 26H, CH_2), 0.88 (t, 3H, J = 6.0 Hz, CH_3). ^{13}C-NMR: δ 115.93, 114.99 (Ar), 78.69 (C-2), 62.75 (C-1), 56.03 (OCH_3).

General Procedure for Methylation of Alcohols. To a stirred solution of the alcohols (1 mmol) in dry DMF (5 mL) was added sodium hydride (2.5 mmol) portionwise at 0 °C. After the mixture was stirred for 30 min, methyl iodide (2.5 mmol) was added. The reaction was stirred at room temperature. Once the reaction was complete, methanol was added at 0 °C to destroy the excess of sodium hydride. The solvent was evaporated under vacuum, and the residue was dissolved in ethyl acetate. The organic solution was washed with water and brine, dried (Na_2SO_4), filtered, and evaporated. This reaction afforded pure products; therefore, chromatographic purification was not necessary except for characterization purposes.

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (13). Compound **11** (1.2 g, 2.84 mmol) was methylated as described above to give **13** as a white solid (1.2 g) in 97% yield after column purification; $[\alpha]_D$ −6.9°; ^{13}C-NMR: δ 115.90, 114.99 (Ar), 78.8 (C-2), 72.02, 71.98, 70.20 (C-1, C-3, OCH_2), 57.88, 56.02 (OCH_3).

1-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol (7). To a solution of **13** (1.0 g, 2.3 mmol) in 4:1 acetonitrile−water (21 mL) was slowly added ammonium cerium(IV) nitrate (2.9 g, 5.5 mmol) at 0 °C with vigorous stirring. The mixture was stirred at room temperature for 1 h. After this time TLC (4:1 hexanes−ethyl acetate) showed complete conversion of **13** into the title compound. The reaction was quenched by the addition of sodium sulfite (1.0 g). The mixture was diluted with ethyl acetate, and the organic solution was washed with water and brine, dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography (6:1 hexane−ethyl acetate) to give **7** (0.853 g, 94%) as a low-melting white solid; $[\alpha]_D$ −9.5°; lit.[10] $[\alpha]_D$ −10.13° (*c* 1.5, $CHCl_3$), lit.[25] $[\alpha]_D$ −9.92° (*c* 1.64, $CHCl_3$), lit.[8] $[\alpha]_D$ −9.46° (*c* 1.64, $CHCl_3$).

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α,*β*-D-glucopyranosyl Trichloroacetimidate (8). To a solution of 1,2-di-*O*-acetyl-3,4,6-tri-*O*-benzyl-*β*-D-glucopyranose[16] (**16**, 1.0 g, 1.87 mmol) in dry DMF (10 mL) was added hydrazine acetate (0.213 g, 2.32 mmol). The mixture was stirred under nitrogen for 4 h. After this time TLC (4:1 hexane-ethyl acetate) showed that the reaction was complete. The mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated to give **18** quantitatively (0.921 g). The crude hemiacetal **18** was pure enough to continue with this procedure. Compound **18** was dried under vacuum for 4 h and then dissolved in dry dichloromethane (30 mL). Trichloroacetonitrile (0.231 mL) and anhydrous potassium carbonate (1.22 g) were added. The mixture was stirred for 3 h under nitrogen. TLC (4:1 hexane−ethyl acetate) showed traces of **18** and the faster-running title compound. The reaction was quenched by filtration of the inorganic base through a pad of Celite 545, and the solvent was evaporated. Crude **8** was then purified through a short column using 8:1 hexanes−ethyl acetate to give the glucosyl donor **8** in 85% yield. ^{1}H-NMR: δ 8.63 (s, 0.46H, NH), 8.56 (s, 0.56H, NH), 7.32−7.15 (m, 15H, 3Ph), 6.52 (d, 0.53H, $J_{1,2}$ = 3.5 Hz, H-1a), 5.74 (d, 0.46H, $J_{1,2}$ = 8.0 Hz, H-1b), 5.29 (dd, 0.46H, $J_{2,3}$ = 9.4 Hz, H-2b isomer), 5.09 (dd, 0.53H, $J_{2,3}$ = 10.0 Hz, H-2a isomer), 1.99 (s, CH_3CO).

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α,*β*-D-mannopyranosyl Trichloroacetimidate (9). Benzylated 1,2-orthoester **15** (3.0 g) was hydrolyzed in 80% HOAc (50 mL) at room temperature for 6 h. After this time, TLC (2:1 hexanes−ethyl acetate) showed complete conversion of **15** into a slower-moving material. Acetic acid was coevaporated under vacuum with toluene to afford pure **17** quantitatively (3.0 g). Hemiacetal **17** was dried under vacuum overnight. Compound **17** was treated with trichloroacetonitrile−potassium carbonate as described for **8** to give the mannosyl donor **9** in 96% yield (3.8 g). ^{1}H-NMR: δ 8.71 (s, NH), 8.63 (s, NH), 7.35−6.78 (m, 15H, 3Ph), 6.29 (d, H-1*β*), 5.89 (d, H-1α), 5.49 (dd, H-2), 4.89−4.47 (m), 4.06−3.68 (m), 2.18 (s, 3H, CH_3).

General Procedure for Glycosylation of 7 with 1,2-*trans*-Glycosyl Donors 8 and 9. A mixture of the glycosyl donor **8** or **9** (1.4 mmol) and the glycosyl acceptor **7** (1.3 mmol) in anhydrous dichloromethane (30 mL) was stirred under dry nitrogen with molecular sieves (3 Å) for 20 min at room temperature. The mixture was cooled at −78 °C, and TMSOTf (50 μmol, 0.035 equiv) was added. Every reaction was complete in 10 min. The Lewis acid was neutralized at room temperature with triethylamine (20 μL). The solvent was evaporated and the crude 1,2-*trans*-glycopyranosides were purified by column chromatography.

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(2′-*O*-acetyl-3′,4′,6′-tri-*O*-benzyl-*β*-D-glucopyranosyl)-*sn*-glycerol (19). Compound **7** (433.3 mg, 1.3 mmol) was glucosylated with **8** (930 mg, 1.4 mmol) to give **19** in 76% yield (805 mg); $[\alpha]_D$ −8.5°; ^{1}H-NMR: δ 7.32−7.15 (m, 15H, 3PhCH_2), 4.99 (dd, 1H, $J_{1',2'}$ = 7.9 Hz, $J_{2',3'}$ = 8.4 Hz, H-2′), 4.78 and 4.66 (2d, 2H, J = 11 Hz, CH_2Ph), 4.78 and 4.54 (2d, 2H, J = 12 Hz, CH_2Ph), 4.63 and 4.54 (2d, 2H, J = 12 Hz, CH_2Ph), 4.49 (d, 1H, H-1′), 3.92−3.35 (12H), 3.41 (s, CH_3O), 1.95 (s, 3H, CH_3CO), 1.59 (m, 4H, $2CH_2$), 1.25 (s, 26H, CH_2), 0.87 (t, 3H, J = 6 Hz, CH_3). ^{13}C-NMR: δ 169.6 (CO), 138.27, 128.41, 127.98, 127.80 (Ph), 101.39 (C-1′), 57.9 (CH_3O), 20.85 (CH_3CO), 14.06 (CH_3).

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(2′-*O*-acetyl-3′,4′,6′-tri-*O*-benzyl-α-D-mannopyranosyl)-*sn*-glycerol (20). Compound **7** (0.871 g, 2.6 mmol) was glycosylated with **9** (1.90 mg, 2.9 mmol) to give the title compound in 87% yield (1.83 g); $[\alpha]_D$ +37.5°; ^{1}H-NMR: δ 7.33−7.12 (m, 15H, 3PhCH_2), 5.37 (dd, 1H, $J_{2',3'}$ = 2.7 Hz, H-2′), 4.86 (d, 1H, $J_{1',2'}$ = 1.6 Hz, H-1′), 4.86 and 4.49 (2d, 2H, J = 11 Hz, CH_2Ph), 4.70 and 4.54 (2d, 2H, J = 11 Hz, CH_2Ph), 4.69 and 4.50 (2d, 2H, J = 12 Hz, CH_2Ph), 2.14 (s, 3H, CH_3CO), 1.54 (t, 2H, J = 6.0 Hz), 1.25 (s, 26H), 0.87 (t, 3H). ^{13}C-NMR: δ 170.39 (CO), 138.50, 132.29, 128.28, 127.55 (Ph), 98.17 (C-1′), 58.07 (CH_3O), 31.90, 29.51, 26.10, 21.07 (CH_2), 14.07 (CH_3).

General Procedure for Deacetylation. Compounds **19** and **20** were deacetylated at room temperature with dry ammonia gas dissolved in dry methanol in 15 min, giving **21** and **22**, respectively. This reaction is quantitative and gives very pure products. Methanol was evaporated, and the alcohols were dried under vacuum and used in the next step.

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(3′,4′,6′-tri-*O*-benzyl-2′-*O*-methyl-*β*-D-glucopyranosyl)-*sn*-glycerol (23). Compound **21** (149 mg) was 2′-*O*-methylated as described above in 97% yield (145 mg); $[\alpha]_D$ −9.7° (*c* 1.2, $CHCl_3$); ^{13}C-NMR: δ 138.89, 138.34, 128.34, 127.93, 127.71, 127.55 (Ph), 103.88 (C-1′), 60.45, 57.88 (CH_3O), 31.95, 29.69, 29.52, 29.35, 26.16, 22.68 (CH_2), 14.06 (CH_3).

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(3′,4′,6′-tri-*O*-benzyl-2′-*O*-methyl-α-D-mannopyranosyl)-*sn*-glycerol (24). Compound **22** (39.6 mg) was methylated in 98% yield (39 mg); $[\alpha]_D$ +38.3°; ^{13}C-NMR: δ 138.89, 138.34, 128.34, 127.93, 127.71, 127.55 (Ph), 98.5 (C-1′), 59.99, 57.80 (CH_3O), 31.95, 29.69, 29.52, 29.35, 26.16, 22.68 (CH_2), 14.06 (CH_3).

General Procedure for Synthesis of Xanthates 25 and 26. Sodium hydride (15 mg, 0.62 mmol) was added to an ice-cold solution of the alcohol (150 mg, 0.32 mmol) and imidazole (4 mg, 0.055 mmol) in dry THF (5 mL). The mixture was stirred for 1 h at room temperature under dry nitrogen, and carbon disulfide (0.32 mmol) was added. Stirring was continued for 20 min, and methyl iodide (2.5 mmol) was added. The reaction was monitored by TLC (3:1 hexanes−ethyl acetate). Complete conversion of the respective alcohol into xanthate **25** or **26** was observed in each reaction. Methanol was added at 0 °C to destroy the excess of sodium hydride. The solvent was evaporated and the residue was dissolved in ether. The organic solution was washed with water, dilute hydrochloric acid, and water, dried (Na_2SO_4), and evaporated. These compounds were used in the next step without further characterization.

General Procedure for Radical Reduction of Xanthates. A solution of *β*-glycoside **25** (precursor to **2**) or α-glycoside **26** (precursor to **3**) (100 mg, 0.117 mmol) in dry toluene (4 mL) was added dropwise to a refluxing solution of

tri-*n*-butyltin hydride (0.31 mL, 1.17 mmol) in dry toluene (2 mL) containing 5 mg of AIBN. The reaction was monitored by TLC (4:1 hexanes−ethyl acetate); when it was complete, the solvent was evaporated and the residue was purified by column chromatography, eluting the column with hexanes first and then with 20:1 hexanes−ethyl acetate, 15:1 hexanes-ethyl acetate, and 10:1 hexanes−ethyl acetate to collect the pure deoxygenated compound **27** or **28**.

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(3′,4′,6′-tri-*O*-benzyl-2′-deoxy-β-D-*arabino*-hexopyranosyl)-*sn*-glycerol (27). Yield, 80 mg (92%); $[\alpha]_D$ −7.1°; ^{1}H-NMR: δ 7.32−7.18 (m, 15H, 3PhCH$_2$), 4.89 (d, 1H, J = 11.0 Hz, OCH$_2$Ph), 4.68 (d, 1H, J = 11.0 Hz, OCH$_2$Ph), 4.63 (d, 2H, J = 11.0 Hz, OCH$_2$Ph), 4.54 (d, 2H, J = 11.0 Hz, OCH$_2$Ph), 4.46 (dd, 1H, $J_{1',2e'}$ = 2.0 Hz, $J_{1',2a'}$ = 9.5 Hz, H-1′), 3.97 (m, 1H, H-5′), 3.73−3.26 (m, 9H), 3.44 (s, OCH$_3$), 2.36 (ddd, 1H, $J_{2e',3'}$ = 5.0 Hz, $J_{2'e,2'a}$ = 12.0 Hz, H-2′e), 1.73−1.43 (m, 5H), 1.25 (s, 26H, CH$_2$), 0.87 (t, 3H, CH$_3$). ^{13}C-NMR: δ 138.46, 128.41, 128.32, 127.97, 127.68, 127.51 (Ph), 100.20 (C-1′), 57.93 (OCH$_3$), 36.68 (C-2′), 31.94, 29.68, 29.52, 29.35, 26.14, 22.67, 14.06.

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(3′,4′,6′-tri-*O*-benzyl-2′-deoxy-α-D-*arabino*-hexopyranosyl)-*sn*-glycerol (28). Yield, 82 mg (94%); $[\alpha]_D$ +25.5°; ^{1}H-NMR: δ 7.32−7.15 (m, 15H, 3PhCH$_2$), 4.97 (dd, 1H, H-1′), 4.89 and 4.52 (d, 2H, J = 11.0 Hz, OCH$_2$Ph), 4.66 and 4.50 (d, 2H, J = 12.0 Hz, OCH$_2$Ph), 4.68 and 4.62 (d, 2H, J = 12.0 Hz, OCH$_2$Ph), 3.98 (m, 1H, H-5′), 1.25 (s, 26H, CH$_2$), 0.87 (t, 3H, CH$_3$). ^{13}C-NMR: δ 138.70, 138.59, 138.16, 128.28, 127.58, 97.82 (C-1′), 58.02 (OCH$_3$), 35.45 (C-2′), 31.90, 29.64, 29.48, 29.31, 26.08, 22.64 (CH$_2$), 14.06 (CH$_3$).

General Procedure To Remove Benzyl Groups. Protected glycosides were dissolved in 1:1 THF−HOAc, and 1−2 equiv (by weight) of palladium on charcoal were added. The mixture was degassed under vacuum, and then hydrogen was let into the reactor. After this process was done three times, the mixture was stirred at room temperature under a balloon pressure of hydrogen. The reaction was usually complete in 4−5 h (TLC, 10:1:0.2 ethyl acetate−methanol−water). The catalyst was filtered through a pad of Celite 545 and washed with a large volume of solvent (1:1 THF−HOAc). The solvents were evaporated under vacuum, and traces of HOAc were coevaporated with distilled toluene. The deprotected glycosides **2**−**6** were purified by column chromatography using a mixture of distilled solvents (10:1 ethyl acetate−methanol). The purified glycosides were then filtered in distilled methanol through lipophilic Sephadex LH-20 to remove low molecular weight impurities such as salts.

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(2′-deoxy-β-D-*arabino*-hexopyranosyl)-*sn*-glycerol (2). Compound **27** (30 mg) was debenzylated to give the title compound in 96% yield (14 mg); $[\alpha]_D$ −14.7°; ^{13}C-NMR: δ 100.3 (C-1′), 78.7 (C-5′), 62.05 (C-6), 58.0 (OCH$_3$), 38.5 (C-2′), 31.95, 29.69, 29.35, 26.11, 22.62 (CH$_2$), 14.09 (CH$_3$). FAB HRMS: Calcd for $C_{26}H_{52}O_7Na$, 499.3611; found 499.3601.

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(2′-deoxy-α-D-*arabino*-hexopyranosyl)-*sn*-glycerol (3). Debenzylation of 2′-deoxy-α-glycoside **28** (35 mg) gave **3** (21 mg) in 94% yield; $[\alpha]_D$ +45.0°; ^{1}H-NMR: δ 4.90 (dd, 1H, $J_{1',2a'}$ = 2.5 Hz, $J_{1',2e'}$ ∼1.0 Hz, H-1′), 3.93 (m, 1H, H-5′), 3.44 (s, 3H, OCH$_3$), 2.15 (ddd, 1H, $J_{2e',3'}$ = 4.7 Hz, $J_{2e',2a'}$ = 11.5 Hz, H-2e′), 1.70 (ddd, 1H, H-2a′), 1.25 (s, 26H, CH$_2$), 0.87 (t, 3H, CH$_3$). ^{13}C-NMR: δ 98.05 (C-1′), 79.33 (C-5′), 62.07 (C-6′), 57.94 (OCH$_3$), 37.36 (C-2′), 31.90, 29.64, 29.48, 29.31, 26.06, 22.67 (CH$_2$), 14.06 (CH$_3$). FAB HRMS: Calcd for $C_{26}H_{52}O_7Na$, 499.3611; found 499.3600.

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(2′-*O*-methyl-β-D-glucopyranosyl)-*sn*-glycerol (4). Compound **23** (142.1 mg) was debenzylated in 96% yield (89 mg) to give **4** as a white amorphous solid; $[\alpha]_D$ −14.7°; ^{13}C-NMR: δ 103.64 (C-1′), 62.36 (C-6′), 60.61, 57.89 (OCH$_3$), 31.90, 29.64, 29.48, 29.31, 26.06, 22.67 (CH$_2$), 14.06 (CH$_3$). FAB HRMS: Calcd for $C_{27}H_{54}O_8Na$, 529.3716; found 529.3717. Calcd for $C_{27}H_{53}O_8$ $(M - H)^+$, 505.3740; found 505.3743.

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(2′-*O*-methyl-α-D-mannopyranosyl)-*sn*-glycerol (5). Compound **24** (39 mg) was debenzylated to afford a white amorphous solid (25 mg, 94%); $[\alpha]_D$ +40.0°; ^{13}C-NMR: δ 98.89 (C-1′), 79.5 (C-5′), 62.13 (C-6′), 60.10, 58.10 (OCH$_3$), 31.90, 29.64, 29.48, 29.31, 26.06, 22.67 (CH$_2$), 14.06 (CH$_3$). FAB HRMS: Calcd for $C_{27}H_{54}O_8Na$, 529.3716; found 529.3702. Calcd for $C_{27}H_{55}O_8$ $(MH)^+$, 507.3897; found 507.3902.

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(α-D-mannopyranosyl)-*sn*-glycerol (6). Compound **22** (40 mg) was debenzylated to give the title compound as a white amorphous solid in 95% yield (25 mg); $[\alpha]_D$ +57.2°; ^{1}H-NMR: δ 4.93 (d, 1H, $J_{1',2'}$ = 1.8 Hz, H-1), 4.10 (m, 1H, H-5′), 1.25 (s, 26H, CH$_2$), 0.87 (t, 3H, CH$_3$). FAB HRMS: Calcd for $C_{27}H_{54}O_8Na$, 529.3716; found 529.3724.

Cell Culture. A549, MCF-7, MCF-7/Adr, HT-29, L1210, Lewis lung, P388, and P388/Adr cell lines were obtained from the DCT Tumor Repository, NCI−Frederick Cancer Research Facility (Frederick, MD). L1210 and L1210/vmdr cells, a murine leukemia cell line transfected with the human mdr 1 gene (pHa MDR1/A), were a generous gift from Dr. Alan C. Sartorelli, Yale University School of Medicine. Cells were cultured in RMPI 1640 (Mediatech) medium supplemented with 10% FBS (Life Technologies). The medium for L1210/vmdr cells contained 0.06 μg/mL colchicine, which was removed one week before the experiments were carried out.

Assay of Growth Inhibition. Cell growth was estimated by in situ fixation of cells, followed by staining with the protein-binding dye sulforhodamine B as described elsewhere.[26] Mouse and human tumor cells were treated with the drugs for 72 h. Stock solutions of the drugs were made in ethanol. The final concentration of ethanol did not exceed 1%. Compound **1** was obtained from Calbiochem.

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