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Convergent *C*-Glycolipid Synthesis via the Ramberg–Bäcklund Reaction: Active Antiproliferative Glycolipids

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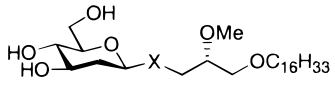
ABSTRACT



14 a X=O antiproliferative
14 b X=CH_2 an active *C*-analog

A novel methodology has been developed, employing the Ramberg–Bäcklund rearrangement and ionic hydrogenation to synthesize *C*-glycosides with high stereoselectivity at the anomeric center. The *C*-glycolipid 14b exhibits antiproliferative properties similar to those of *O*-glycoside analogue 14a.

In the field of *C*-glycoside synthesis,[1] *C*-glycolipids are becoming interesting targets. Recent papers report linear syntheses of *C*-glycolipids from simple *C*-glycofragments.[2] Two groups, ours[3] and Taylor's,[4] simultaneously described a new convergent procedure for preparing *C*-glycosides via exo-glycals, which are derived from sulfonyl glycosides using the Ramberg−Bäcklund (RB) rearrangement. The key step for both groups was the formation of an exo-glycal using a one-pot procedure originally developed by Meyers,[5] which uses a halocarbon and base—in our examples, CF_2Br_2 and KOH/Al_2O_3 at room temperature.[6] We found that the RB conditions using CF_2Br_2 (bp 23 °C) failed to afford good yields of the RB product, if the sulfones did not have one benzylic group. The simple expedient of using CF_2BrCF_2Br (bp 47 °C) at reflux solved this problem,[7] as we now describe.

We first turned our attention to the use of exo-glycals for the convergent preparation of the model *C*-glycolipid **5**. In

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(7) Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **1999**, *38*, 2939−2942. This article reports the use of CCl_4 at 60 °C to solve the reactivity problem. However, earlier works report contamination of the RB alkenes with dichlorocyclopropanes formed from the decomposition of CCl_4.

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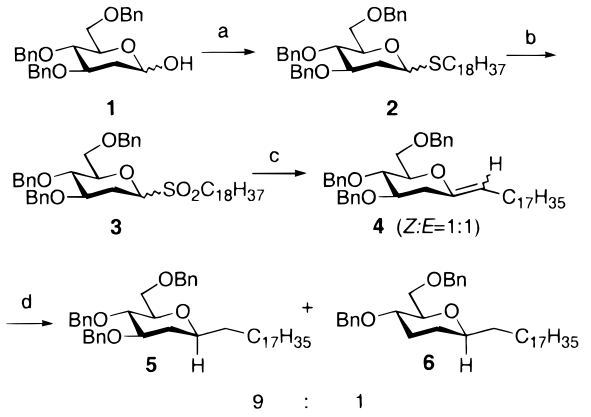
our synthesis (Scheme 1), the benzylated thioglycoside **2** was made from the benzylated 2-deoxyglucose derivative **1** via

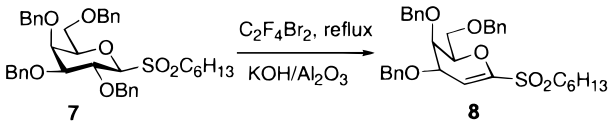
Scheme 1[a]



[a] Reagents and conditions: (a) (1) $CH_3OCH_2CO_2H$, DCC, ether, 87%, (2) $C_{18}H_{37}SH$, $Yb(OTf)_3$, CH_3CN, 60 °C, 89%; (b) MMPP, EtOH/THF/H_2O, 55 °C, 95%; (c) $C_2F_4Br_2$, KOH/Al_2O_3, reflux; (d) Et_3SiH, TFA, CH_2Cl_2, −70 °C.

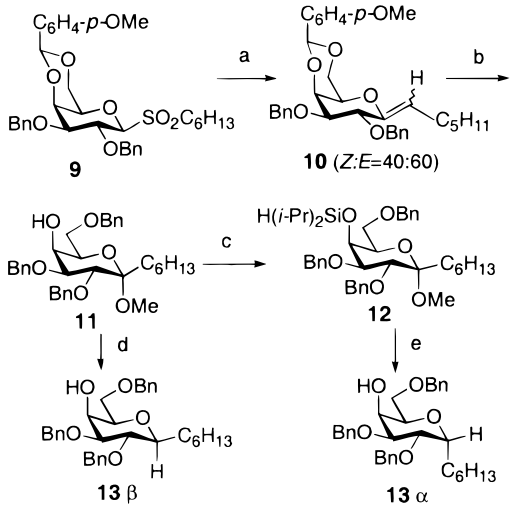
the Inanaga−$Yb(OTf)_3$ method.[8] The sulfide **2** was oxidized using MMPP to form sulfone **3** in good yield. Initial attempts with Chan's variation[6] of the one-pot RB conditions, using CF_2Br_2 and KOH/Al_2O_3, failed. When CF_2BrCF_2Br was used at reflux in place of CF_2Br_2, the reaction worked quite well with β-sulfone to afford the RB alkene **4** in 85% yield (*Z*:*E* = 1:1). For the anomeric α-sulfone **3**, there was very little RB reaction, with the recovered material being unchanged. The product enol ether **4** was a fairly sensitive material; therefore, it was reduced by ionic hydrogenation using Et_3SiH/TFA at −70 °C[9] to afford **5** in 60% yield and overreduced **6** in 7% yield. It was observed that the product **6**, due to the Ferrier rearrangement[10] before reduction, was the major product when the reaction temperature was increased to −20 °C.

A challenging test of the CF_2BrCF_2Br reflux modification was the galactose-derived sulfone **7**. Here our conditions led to elimination, forming endocyclic sulfonylglycal **8** with no trace of the desired RB product. It should be noted that, in



our earlier work,[3] neither mannose- nor glucose-derived sulfones gave elimination when treated with the CF_2Br_2 (bp 23 °C) reagent. We reasoned that a distortion of the galactose ring must have occurred so as to put the 2-benzyloxy group in an axial location so that it could be eliminated. Therefore, we prepared the bicyclic galactosyl sulfone **9** as shown in Scheme 2 on the basis of the assumption that any twisting

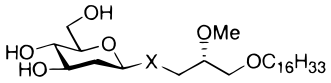
Scheme 2[a]



[a] Reagents and conditions: (a) $C_2F_4Br_2$, KOH/Al_2O_3, reflux, 83%; (b) (1) TMSCl, MeOH, 64%, (2) NaH, 1 equiv of BnBr, THF, 65%; (c) *i*-Pr_2SiHCl, CH_2Cl_2, imidazole, 80%; (d) (1) Ac_2O, pyridine, DMAP, 93%, (2) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 20 °C, 95%, (3) K_2CO_3, MeOH, 95%; (e) CH_2Cl_2, TFA/$BF_3{\cdot}Et_2O$ (4:1), 64%.

or flipping motion necessary to force the 2-benzyloxy group axial would be difficult. With this modification, the RB reaction took place in good yield to form **10**. This material could then be processed to form either α- or β-*C*-glycoside stereoselectively. Thus, intermolecular ionic hydrogenation conditions cleanly produced β-*C*-glycoside **13**β. Alternatively, intramolecular hydride transfer from **12**, the hydrosilylation product of **11**, afforded α-*C*-glycoside **13**α.[9]

Application of our methodology to the preparation of the *C*-glycolipid **14b** of 2-deoxyglucosyl glyceride was an important goal of this work. *O*-Glycolipid **14a** is an active



14 a X=O, **14 b** X=CH_2

analogue of the antiproliferative lead compound ET-18-OCH_3 (edelfosine),[11] which itself is a platelet-activating factor analogue. *O*-Glycolipid **14a** was found to specifically inhibit the growth of tumor cells, tumor cell invasion, and metastasis.[12] Our rationale for preparing *C*-glycoside **14b** was to enhance the metabolic stability compared to **14a**, and our hope was that there would not be a significant decrease of antiproliferative activity.

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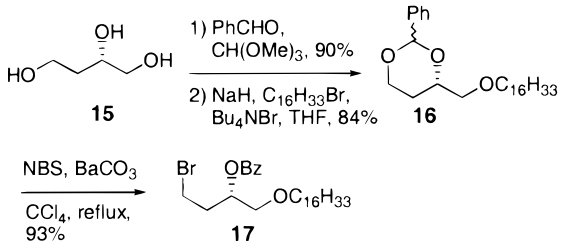
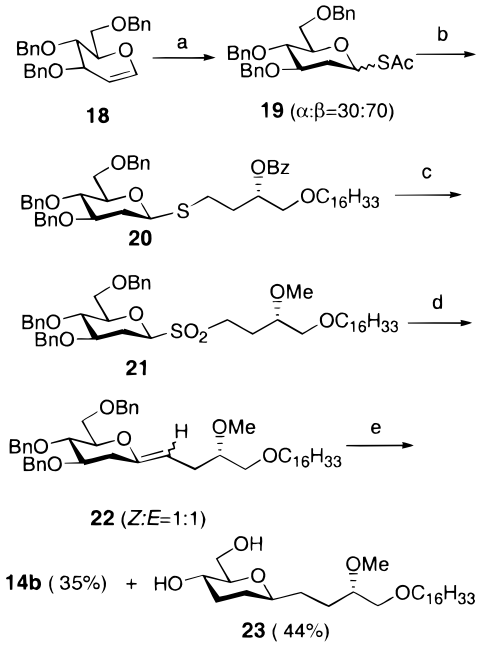
The synthesis of the lipid (*S*)-4-*O*-hexadecyl-3-*O*-benzoyl-1-bromobutane (**17**) was easily accomplished (Scheme 3)

Scheme 3



with (*S*)−(−)-1,2,4-butanetriol (**15**) as starting material. This procedure is based on selective protection of **15** followed by alkylation. Ether **16** was treated with NBS and $BaCO_3$ at reflux to afford bromide **17** in good yield.[13] The thioacetate **19** can be made easily in two steps[14,15] from glucal **18**. The bromide **17** was treated with thioacetate **19** in cysteamine and dithioerythritol (DTE)[16] to afford a separable α and β mixture (α:β = 30:70) of thioglycoside **20** in 64% yield (Scheme 4). Deprotection using NaOMe, followed by *O*-

Scheme 4[a]



[a] Reagents and conditions: (a) (1) HCl, toluene, (2) KSAc, HMPA, 74%; (b) **17**, cysteamine, DTE, HMPA, 64%; (c) (1) NaOMe, MeOH, 96%, (2) NaH, MeI, THF, 90%, (3) MMPP, 55 °C, 94%; (d) $C_2F_4Br_2$, KOH/Al_2O_3, reflux, 60%; (e) (1) Et_3SiH, TFA, −70 °C, (2) H_2, 10% Pd/C, MeOH.

methylation and oxidation, afforded sulfone **21**. The Ramberg−Bäcklund rearrangement of **21** proceeded smoothly with β-sulfone to afford alkene **22** (*Z*:*E* = 1:1) in 60% yield.[17] Ionic hydrogenation followed by separation of the products and debenzylation proceeded to form both 2-deoxy *C*-glycolipid **14b** and 2,3-dideoxy *C*-glycolipid **23**.[18]

Table 1 presents the data for the in vitro biological evaluation of the growth inhibitory properties of *O*-glycoside

Table 1. Growth Inhibitory Properties of **14a**,**b** and **23**: IC_{50} Values for Inhibition of Cell Proliferation[a]

	IC_{50} (μM)		
breast cancer cell line	**14a**	**14b**	**23**
MCF-7	6.93[12]	25.6	21.2
MDA-MB-435		12.2	21.9
MDA-MB-468		34.4	24.2
MDA-MB-231		40.0	27.8

[a] The IC_{50} values for **14b** and **23** were determined as described in ref 19. Briefly, exponentially growing cells were incubated with the drugs (0−60 μM), and the increase in cell numbers after 48 h was determined and expressed as a percentage of the controls, which had no drug. The IC_{50} value for **14a** was determined after a 72 h incubation period using the sulforhodamine assay described in ref 12.

14a, *C*-glycoside **14b**, and *C*-glycoside **23** on human tumor cells. The IC_{50} values[19] (drug concentrations required to inhibit growth by 50%) indicate that the *C*-glycoside analogues show antiproliferative properties similar to those of *O*-glycoside analogue **14a**. Thus, the activities are not dependent on the glycosidic oxygen in the drug.

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(17) Representative Ramberg−Bäcklund rearrangement: preparation of exo-glycal **22**. A sample of sulfone **21** (0.135 g, 0.16 mmol, β-isomer) was dissolved in 3 mL of $C_2F_4Br_2$ and 1 mL of *t*-BuOH at 47 °C. Then KOH/Al_2O_3 (0.25 g, 50 wt %) was added. The reaction mixture was heated at reflux for 6 h. The mixture was filtered through a pad of Celite, and the solids were washed with CH_2Cl_2. The residue was purified by column chromatography on silica gel, with 10% EtOAc−PE as eluent, to afford 74 mg (60%) of alkene **22** (*Z*:*E* = 1:1).

(18) *C*-Glycolipid **14b**: white solid, mp 62−64 °C. $[\alpha]_D = -3.47°$ (*c* = 1.5, $CHCl_3$). Anal. Calcd for $C_{27}H_{54}O_6$: C, 68.35; H, 11.39. Found: C, 68.12; H, 11.12. ^{1}H NMR (500 MHz, CD_2Cl_2): δ 3.80 (dd, H, *J* = 3.2, 11.4 Hz, H_6), 3.69 (dd, 1H, *J* = 5.1, 11.4 Hz, H_6), 3.61 (m, 1H, H_3), 3.45 (m, 1H, H_1), 3.42−3.38 (m, 4H), 3.35 (s, 3H, $-OCH_3$), 3.29 (m, 2H), 3.22 (m, 1H, H_5), 2.47 (broad peak), 2.00 (dd, 1H, *J* = 4.8, 12.5 Hz, H_2), 1.63−1.48 (m, 9H), 1.34−1.29 (m, 26H), 0.88 (t, 3H, *J* = 7.0 Hz, CH_3). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 80.53, 79.81, 76.29, 73.60, 73.49, 73.36 (C-1), 72.20, 63.18, 57.91, 39.84, 32.61, 31.99, 30.39, 30.20, 30.04, 28.39, 26.83, 23.38, 14.56. *C*-Glycolipid **23**: white solid, mp 47−48 °C. Anal. Calcd for $C_{27}H_{54}O_5$: C, 70.69; H, 11.86. Found: C, 70.48; H, 11.65. ^{1}H NMR (500 MHz, C_6D_6):δ 3.77 (m, 1H), 3.70 (m, 1H), 3.42 (m., 2H), 3.34−3.30 (m, 4H), 3.27 (s, 3H, $-OCH_3$), 3.23 (m, 1H), 3.14 (m, 1H), 1.93 (broad peak), 1.73−1.54 (m, 8H), 1.41−1.05 (m, 30H), 0.87 (t, 3H, $-CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.99, 80.64, 77.97, 73.44, 72.42, 68.56, 64.33, 58.26, 33.43, 32.69, 32.07, 31.69, 30.40, 30.25, 30.12, 28.44, 26.90, 23.46, 14.89.

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