

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

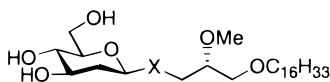
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ABSTRACT



14 a X=O antiproliferative
14 b X=CH₂ 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, ours³ 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, CF₂Br₂ and KOH/Al₂O₃ at room temperature.⁶ We found that the RB conditions using CF₂Br₂ (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 CF₂BrCF₂Br (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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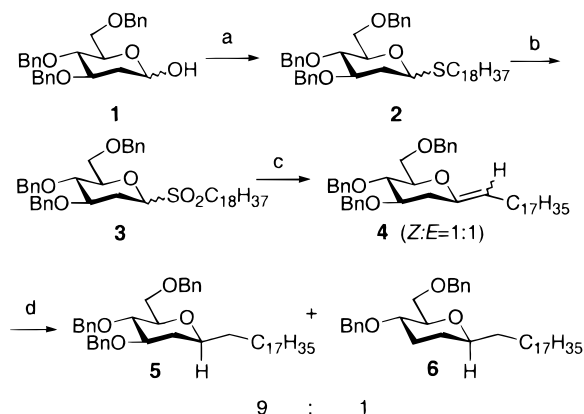
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(7) Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **1999**, *38*, 2939–2942. This article reports the use of CCl₄ at 60 °C to solve the reactivity problem. However, earlier works report contamination of the RB alkenes with dichlorocyclopropanes formed from the decomposition of CCl₄.

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

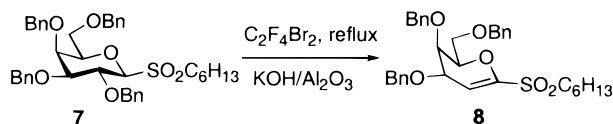
Scheme 1^a



^a Reagents and conditions: (a) (1) $\text{CH}_3\text{OCH}_2\text{CO}_2\text{H}$, DCC, ether, 87%, (2) $\text{C}_{18}\text{H}_{37}\text{SH}$, $\text{Yb}(\text{OTf})_3$, CH_3CN , 60 °C, 89%; (b) MMPP, $\text{EtOH}/\text{THF}/\text{H}_2\text{O}$, 55 °C, 95%; (c) $\text{C}_2\text{F}_4\text{Br}_2$, $\text{KOH}/\text{Al}_2\text{O}_3$, reflux; (d) Et_3SiH , TFA, CH_2Cl_2 , -70 °C.

the Inanaga– $\text{Yb}(\text{OTf})_3$ method.⁸ The sulfide **2** was oxidized using MMPP to form sulfone **3** in good yield. Initial attempts with Chan's variation⁶ of the one-pot RB conditions, using CF_2Br_2 and $\text{KOH}/\text{Al}_2\text{O}_3$, failed. When $\text{CF}_2\text{BrCF}_2\text{Br}$ 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 $\text{Et}_3\text{SiH}/\text{TFA}$ at -70 °C⁹ to afford **5** in 60% yield and overreduced **6** in 7% yield. It was observed that the product **6**, due to the Ferrier rearrangement¹⁰ before reduction, was the major product when the reaction temperature was increased to -20 °C.

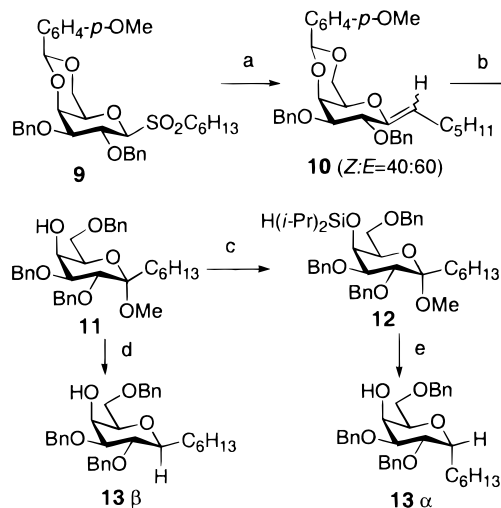
A challenging test of the $\text{CF}_2\text{BrCF}_2\text{Br}$ reflux modification was the galactose-derived sulfone **7**. Here our conditions led to elimination, forming endocyclic sulfonylglycal **8** with no trace of the desired RB product. It should be noted that, in



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

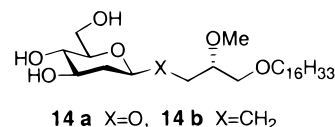
Scheme 2^a



^a Reagents and conditions: (a) $\text{C}_2\text{F}_4\text{Br}_2$, $\text{KOH}/\text{Al}_2\text{O}_3$, reflux, 83%; (b) (1) TMSCl , MeOH , 64%, (2) NaH , 1 equiv of BnBr , THF , 65%; (c) $i\text{-Pr}_2\text{SiHCl}$, CH_2Cl_2 , imidazole, 80%; (d) (1) Ac_2O , pyridine, DMAP, 93%, (2) Et_3SiH , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , 20 °C, 95%, (3) K_2CO_3 , MeOH , 95%; (e) CH_2Cl_2 , TFA/ $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (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 **13β**. Alternatively, intramolecular hydride transfer from **12**, the hydrosilylation product of **11**, afforded α -C-glycoside **13α**.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



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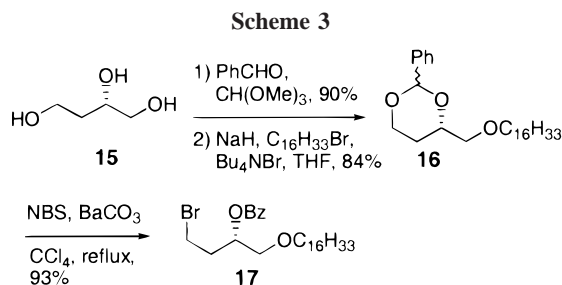
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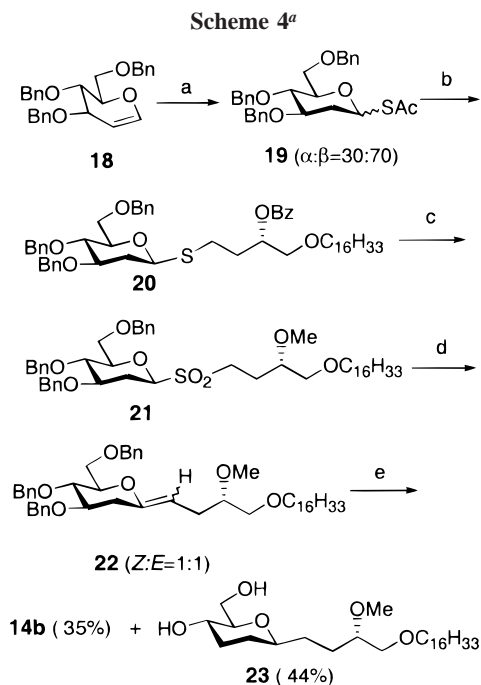
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The synthesis of the lipid (*S*)-4-*O*-hexadecyl-3-*O*-benzoyl-1-bromobutane (**17**) was easily accomplished (Scheme 3)



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 BaCO₃ 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*-



^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) C₂F₄Br₂, KOH/Al₂O₃, reflux, 60%; (e) (1) Et₃SiH, TFA, –70 °C, (2) H₂, 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 debenzoylation 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**: IC₅₀ Values for Inhibition of Cell Proliferation^a

breast cancer cell line	IC ₅₀ (μ M)		
	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 IC₅₀ values for **14b** and **23** were determined as described in ref 19. Briefly, exponentially growing cells were incubated with the drugs (0–60 μ M), and the increase in cell numbers after 48 h was determined and expressed as a percentage of the controls, which had no drug. The IC₅₀ 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 IC₅₀ values¹⁹ (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 C₂F₄Br₂ and 1 mL of *t*-BuOH at 47 °C. Then KOH/Al₂O₃ (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 CH₂Cl₂. 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. [α]_D = –3.47° (*c* = 1.5, CHCl₃). Anal. Calcd for C₂₇H₅₄O₆: C, 68.35; H, 11.39. Found: C, 68.12; H, 11.12. ¹H NMR (500 MHz, CD₂Cl₂): δ 3.80 (dd, H, *J* = 3.2, 11.4 Hz, H₆), 3.69 (dd, 1H, *J* = 5.1, 11.4 Hz, H₆), 3.61 (m, 1H, H₃), 3.45 (m, 1H, H₁), 3.42–3.38 (m, 4H), 3.35 (s, 3H, –OCH₃), 3.29 (m, 2H), 3.22 (m, 1H, H₅), 2.47 (broad peak), 2.00 (dd, 1H, *J* = 4.8, 12.5 Hz, H₂), 1.63–1.48 (m, 9H), 1.34–1.29 (m, 26H), 0.88 (t, 3H, *J* = 7.0 Hz, CH₃). ¹³C NMR (75 MHz, CD₂Cl₂): 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 C₂₇H₅₄O₅: C, 70.69; H, 11.86. Found: C, 70.48; H, 11.65. ¹H NMR (500 MHz, C₆D₆): δ 3.77 (m, 1H), 3.70 (m, 1H), 3.42 (m, 2H), 3.34–3.30 (m, 4H), 3.27 (s, 3H, –OCH₃), 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, –CH₃). ¹³C NMR (75 MHz, CDCl₃): 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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