JOC Notes

A General and Stereoselective Route to α- or β-Galactosphingolipids via a Common Four-Carbon Building Block

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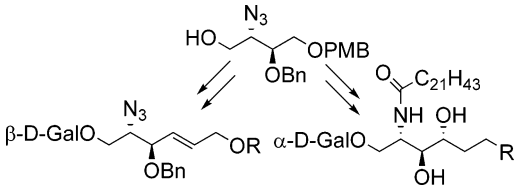

A general synthetic strategy toward α- or β-galactosylceramides and their analogues from 3-azido-2-*O*-benzyl-1-*O*-(4-methoxybenzyl)butane-1,2,4-triol is described. The key steps for the installation of the main lipid chain are either a diasteroselective alkynylation reaction yielding the 4*R* stereocenter of phytosphingosine or a Wittig olefination generating the trans double bond of sphingosine. The methodology allows the preparation of different glycolipids with variations in the structure of the sphingoid base. In particular, three α-GalCer-related compounds have been synthesized and evaluated for their ability to activate CD1d-restricted T-cells.

CD1 proteins are a family of highly conserved molecules that bind and display a variety of lipids, glycolipids, and lipopeptides to T lymphocytes.[1] In humans, there are five known isoforms, CD1a, CD1b, CD1c, CD1d, and CD1e, while the mouse has only CD1d. The best characterized lipids involved in CD1-restricted antigen presentation to T cells are galactosylceramides, potent stimulators of the mammalian immune system. Among these, KRN7000 (**1**, Figure 1), the synthetic analogue of agelasphin (isolated from a marine sponge), is an α-galactosylphytosphingosine derivative (α-GalCer) that binds to CD1d molecules on antigen presenting cells and is a powerful immunostimulant of type I natural killer T (iNKT) cells.[2,3] iNKT cells release proinflammatory (Th1) and immunomodulatory (Th2) cytokines upon activation, which can differently influence the immune response to several diseases including tumors, atherosclerosis, infections, and autoimmunity.[4] Structure−activity relationship studies of KRN7000 analogues revealed that it is possible to bias the NKT cells response to α-GalCer to either a Th1 or a Th2 response with potential medical application.[5]

Another galactosylceramidic CD1 antigen is sulfatide (**2**, Figure 1), a mixture of 3-sulfated β-D-galactosylceramides with a D-*erythro*-sphingosine sphingoid base and different fatty acids at the ceramide moiety. Sulfatide is a self-antigen, found in myelin, and presented by all human CD1 family members to specific T cells.[6] Recent studies have demonstrated that the immunogenicity of sulfatide depends both on the length of the ceramide acyl chain and the position of the sulfate group or the nature of the glycosidic linkage.[7]

The studies on KRN7000 and sulfatide outlined above demonstrate the importance of the antigen structure for the immune responses of these molecules. Differences in biological activities have been postulated to be associated with alteration of CD1−lipid complex stability. Thus, the availability of KRN7000 or sulfatide structural analogues provides a useful tool for further expanding our understanding on biological issues, investigating the mechanism involved in CD1-mediated antigen presentation, or developing methods for more selective activations of T cells.

In this study, we report a flexible approach to glycosphingolipid analogues, synthesized in a modular way which allows

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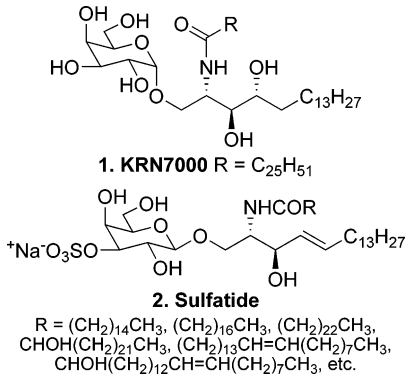


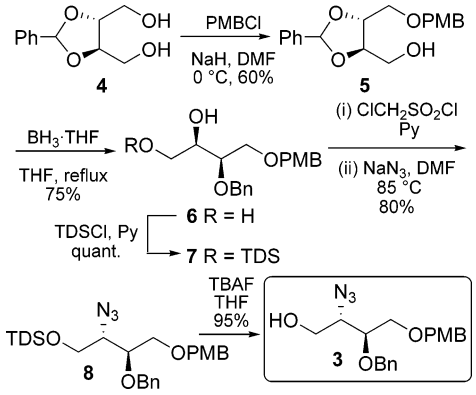
FIGURE 1. Structure of KRN7000 and sulfatide.

us to independently vary the structure of the lipid moiety and the configuration of the glycosidic bond.[8]

We focused our attention on the synthesis of the α-GalCer **15a** and two structurally related compounds **15b** and **15c**, bearing a shorter branched and an aromatic chain, respectively. To verify whether the modification of the linear alkyl chain of the sphingoid tail affects biological activities, the newly synthesized compounds have been evaluated for their ability to activate CD1d-restricted T-cell (a mouse iNKT cell hybridoma). Moreover, the approach toward *β*-glycolipids with a sphingosine-like backbone was successfully explored obtaining the allylic alcohol **22**, a key precursor for oxa-sulfatide analogues.

Our strategy is based on the common precursor **3** that could be easily converted into different structurally related compounds. The great scenario of glycolipid structures accessible from compound **3** is because, once glycosylated, it opens the possibility to obtain the motif of the main natural sphingoid bases (phytosphingosine, sphingosine, and sphinganine). So, by changing the configuration of the glycosidic bond or the character of the sphingoid motif, different classes of natural or modified glycolipid structures are accessible. Here, our general approach is applied to the conversion of compound **3** into derivatives structurally related to KRN7000 and sulfatide. The retrosynthetic plan (see the scheme in the Supporting Information), shows that protected azido triol **3** possesses a primary OH group which could be glycosylated to obtain either α- or *β*-galactosyl derivatives. The α-glycosylated adduct is the proper substrate for the obtainment of phytosphingosine glycolipids through the Carreira enantioselective addition of terminal alkynes to aldehydes, which was previously successfully exploited by us in the synthesis of the sphingoid skeleton.[9] On the other hand, the *β*-glycosylated adduct could be easily transformed, after the introduction of the trans double bond via Wittig olefination, in a precursor of a series of sulfated *β*-D-galactosyl-oxa-ceramides, i.e., analogues bearing an oxygen atom in place of a methylene group in the sphingosine backbone.

SCHEME 1. Synthesis of the Common Intermediate 3



In both cases, a variety of lipid moieties could be easily attached, thus allowing for the synthesis of a wide variety of analogues, differing in the sphingoid chain, that have not been prepared previously.

The centerpiece of our synthetic route is the common precursor **3** which was prepared using commercially available (2*R*,3*R*)-2,3-*O*-benzylidene-D-threitol **4** as the starting material (Scheme 1). Compound **4** was treated with 1 equiv of *p*-methoxybenzyl chloride in the presence of sodium hydride to give the monobenzylated derivative **5**, which was subjected to a regioselective reductive cleavage with borane tetrahydrofuran complex yielding 1,2-diprotected tetrol **6**. Selective silylation of the primary alcohol followed by activation of the remaining hydroxyl of **7** with chloromesyl chloride and azide displacement afforded compound **8** in 80% yield. The desired intermediate **3** was finally obtained after selective deprotection of the silyl ether with tetrabutylammonium fluoride.

With building block **3** in hand, the strategy (Scheme 2) toward α-glycolipids was first developed by taking into consideration the one-pot α-glycosylation protocol of Kobayashi.[10] The reaction, based on a halide ion-catalytic mechanism, consisted in the in situ generation of the galactosyl bromide by reaction of tetrabenzylgalactose **9** with carbon tetrabromide (CBr_4) and triphenylphosphine (Ph_3P), known as Appel agents, followed by coupling with acceptor **3** in the presence of *N*,*N*-tetramethylurea. Purification by flash chromatography allowed recovery of the α-glycosylated product **10** in high yield (85%). The stereochemistry of the anomeric linkage was unambiguously assigned by ^{1}H NMR analysis. The *p*-methoxybenzyl group of compound **10** was then deprotected, and the primary alcohol of **11** was oxidized under Swern conditions to give aldehyde **12** which was the substrate for the Carreira alkynylation.[11]

We first examined the asymmetric alkynylation of compound **12** with tetradecyne to produce the "natural" C-18 sphingoid chain. We expected high stereoselectivity by the prominent stereodifferentiating ability of the Carreira protocol and also convenient stereocontrol by changing only the chiral ligand. In fact, by carrying out the addition reaction in the presence of zinc trifluoromethanesulfonate and (−)-*N*-methylephedrine as chiral additive, we were able to obtain the propargylic alcohol **13a** in 65% yield.[12] The *R* configuration for the new stereocenter was expected because of the use of (−)-*N*-methylephedrine, and

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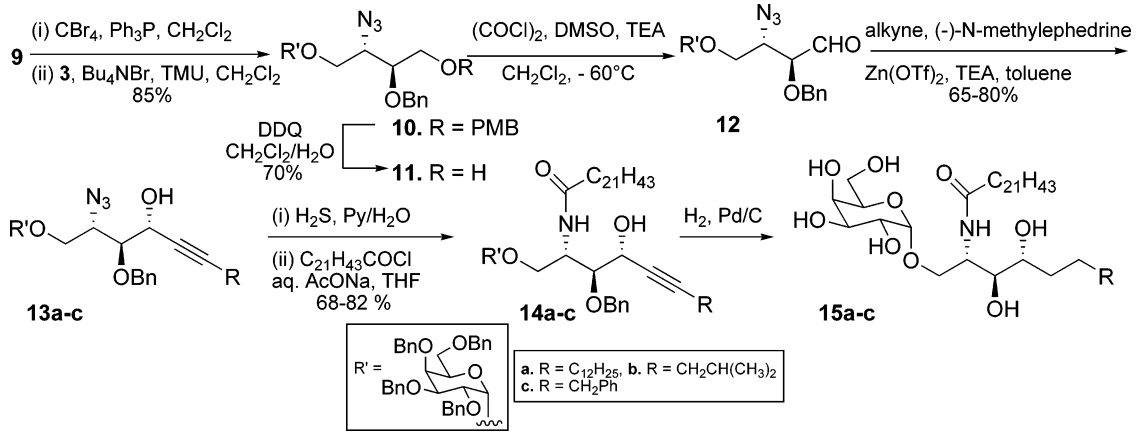
SCHEME 2. Synthesis of α-Galactosyl Glycolipids 15a−c from Common Precursor 3



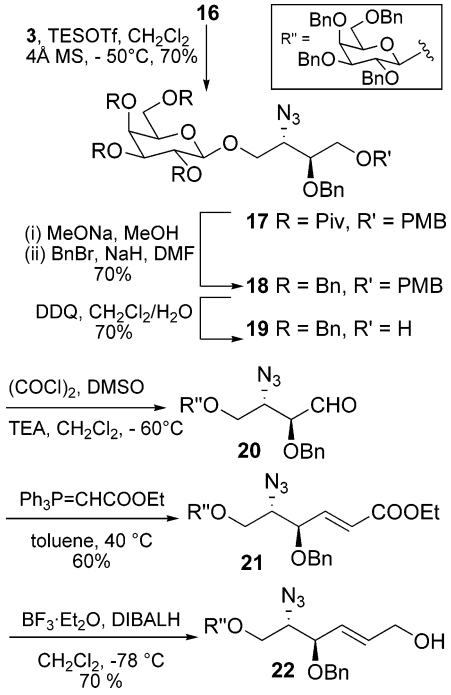
this was confirmed by preparation of the (*R*)- and (*S*)-MTPA esters of **13a** and analysis of their ^{1}H NMR spectra (see the Supporting Information).[13]

The azido group of compound **13a** was then reduced with hydrogen sulfide in pyridine−water, followed by introduction of the fatty acid chain to give **14a**.[7a] Finally, simultaneous reduction of the triple bond and hydrogenolysis of the benzyl groups in the presence of palladium over charcoal gave product **15a**.

The same synthetic steps were followed for the preparation of analogues **15b** and **15c** from aldehyde **12**, the only difference being the alkyne used in the alkynylation reaction. Compounds **15b** and **15c** were obtained in more than satisfactory yield and were fully characterized before biological testing.

The strategy toward β-glycolipids was then examined (Scheme 3). Glycosylation of compound **3** with known pivaloylated trichloroacetimidate **16**[14] at −50 °C in the presence of triethylsilyl trifluoromethanesulfonate as a catalyst afforded β-galactoside **17** in 70% yield. The β-configuration of compound **17** was easily assigned on the basis of the typical 8.0 Hz value for the trans-diaxial $J_{1',2'}$ coupling constant of the anomeric hydrogen. Before proceeding with the chain elongation, it was necessary to exchange the ester protecting groups of galactose for benzyl ethers in order to avoid any problem during the planned reduction of ester **21**. So, compound **17** was subjected to Zèmplen transesterification followed by benzylation to produce galactoside **18**. The *p*-methoxybenzyl ether of compound **18** was selectively removed by treatment with DDQ to obtain **19** which was oxidized under Swern conditions. A Wittig olefination using (carbethoxymethylene)triphenyl-phosphorane led to the E-unsaturated ester **21**, which produced the corresponding allyl alcohol **22** upon reduction with DIBALH at −78 °C. Compound **22** is an useful intermediate for development of new analogues. In fact, through simple alkylation it is a significant precursor of oxa-analogues of β-GalCers, e.g., the precursor of oxa-sulfatides. By varying the alkylating agent, it

SCHEME 3. Synthesis of β-Galactosyl Glycolipids from Common Precursor 3



is possible to easily modify the length of the sphingoid skeleton, generating glycolipid libraries. For our own purposes, we terminated the process at this stage even if it is possible to easily continue with standard procedures (alkylation, azide reduction−amide bond formation, debenzylation with sodium in ammonia, and selective sulfation of position 3 of the sugar).[7a,c]

The biological activities of compounds **15a**−**c** were determined by using a T-cell antigen presentation assay. KRN7000 was used as positive control for validation of the biological assay. Briefly, bone-marrow-derived mouse dendritic cells (DC, 5×10^4/well) were preincubated (2 h) with increasing concentrations (0.003−30 μg/mL) of each compound and used as antigen presenting cells (APC). Mouse FF13 iNKT hybridoma cells (10^5/well), previously generated and characterized,[15] were used as responder cells, and their activation was evaluated by

(12) For our synthetic purposes we only isolated the major product, having the proper *R*-configuration. Therefore, the diasteroselectivity of the reaction was not investigated.

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measuring the release of IL-2 by ELISA 24 h later. Figure 2 (see the Supporting Information) shows that all compounds were active in inducing IL-2 release in a concentration-dependent manner and possess different potencies as compared to KRN7000. This might be ascribed to the fact that NKT cells may very efficiently discriminate lipids with different acyl chain length. Thus, the carbon truncation of the amide chain is sufficient to dramatically reduce cytokine release. The lower immunogenicity of the **15a**−**c** compounds than KRN7000 might be related to a lower TCR binding affinity to CD1d−lipid complexes and to the formation of less stable immunological synapse, as recently demonstrated.[16]

In conclusion, azido triol **3** is a versatile building block for glycosphingolipid synthesis. In fact, after glycosylation it allows the access to a diverse array of sphingoid bases. Here we have reported a new scheme for synthesizing biologically active α-GalCer related compounds. The in vitro characterization of their activities shows that despite main differences in the sphingoid chain, compounds **15a**−**c** possess similar potencies and efficacies.

In addition, we have shown that an alternative functionalization of compound **3** provides access to *β*-GalCer related glycolipids. Moreover, the direct alkylation of compounds **11** or **19** would allow for the preparation of families of α- or *β*-glycosyl-oxa-sphinganines. From this picture, we see that the lipid chains can be easily modified and the glycoconjugate structures altered by use of different starting sugars or glycosylation conditions. Thus, the flexibility of our approach permits the synthesis of different glycolipid derivatives and provides a powerful tool for analogues development and elucidation of their biological functions.

Experimental Section

(2*S*,3*S*,4*R*)-2-Docosanoylamino-1-(α-D-galactopyranosyloxy)-3,4-octadecanediol (15a). Prepared from 0.15 g (0.12 mmol) of compound **14a** according to the general procedure (see the Supporting Information). **15a** (0.063 g, 65%): $[\alpha]_D = +40.0$ (*c* 0.5, pyridine); ^{1}H NMR (C_5D_5N) δ 0.85 (t, 6 H, $J = 7.0$ Hz), 1.16−1.44 (m, 58 H), 1.63−1.95 (m, 5 H), 2.23−2.31 (m, 1 H), 2.38−2.48 (m, 2 H), 4.28−4.34 (m, 2 H), 4.36−4.45 (m, 4 H), 4.50 (dd, 1 H, $J = 6.0$, 6.0 Hz), 4.54 (d, 1 H, $J = 3.0$ Hz), 4.62−4.69 (m, 2 H), 4.80−5.15 (br s, 6H), 5.22−5.28 (m, 1 H), 5.56 (d, 1 H, $J = 3.5$ Hz), 8.45 (d, 1 H, $J = 8.0$ Hz); ^{13}C NMR (C_5D_5N) δ 14.0, 22.7, 26.1, 26.2, 29.3−30.1 (28 C), 31.9, 34.1, 36.5, 51.2, 62.4, 68.4, 70.1, 70.7, 71.4, 72.2, 72.8, 76.5, 101.3, 173.0; ESI-MS *m*/*z* = 824.7 (100) $[M + Na]^+$, 1626.7 (95) $[2M + Na]^+$. Anal. Calcd for $C_{46}H_{91}NO_9$ (801.67): C, 68.87; H, 11.43; N, 1.75. Found: C, 68.83; H, 11.40; N, 1.76.

(2*S*,3*S*,4*R*)-2-Docosanoylamino-8-methyl-1-(α-D-galactopyranosyloxy)-3,4-nonanediol (15b). Prepared from 0.15 g (0.13 mmol) of **14b** according to the general procedure (see the Supporting Information). **15b** (0.064 g, 70%): $[\alpha]_D = +58.0$ (*c* 0.5, pyridine); ^{1}H NMR (C_5D_5N) δ 0.78 (d, 6 H, $J = 6.5$ Hz), 0.85 (t, 3 H, $J = 7.0$ Hz), 1.15−1.92 (m, 44 H), 2.16−2.26 (m, 1 H), 2.37−2.47 (m, 2 H), 4.26−4.32 (m, 2 H), 4.35−4.45 (m, 4 H), 4.50 (dd, 1 H, $J = 6.0$, 6.0 Hz), 4.54 (d, 1 H, $J = 3.5$ Hz), 4.62−4.70 (m, 2 H), 5.23−5.29 (m, 1 H), 5.57 (d, 1 H, $J = 3.5$ Hz), 5−60-5.90 (br s, 6H), 8.44 (d, 1 H, $J = 8.0$ Hz); ^{13}C NMR (C_5D_5N) δ: 14.0, 22.4, 22.5, 22.6, 23.9, 26.1, 28.0, 29.3−29.8 (15 C), 30.2, 31.9, 34.3, 36.5, 39.3, 51.2, 62.4, 68.4, 70.1, 70.7, 71.4, 72.2, 72.8, 76.5, 101.3, 173.0; ESI-MS *m*/*z* = 712.6 $[M + Na]^+$. Anal. Calcd for $C_{38}H_{75}NO_9$ (689.54): C, 66.15; H, 10.96; N, 2.03. Found: C, 66.19; H, 10.97; N, 2.06.

(2*S*,3*S*,4*R*)-2-Docosanoylamino-1-(α-D-galactopyranosyloxy)-7-phenyl-3,4-heptanediol (15c). Prepared from 0.15 g (0.13 mmol) of **14c** according to the general procedure (see the Supporting Information). **15c** (0.065 g, 70%): $[\alpha]_D = +48.0$ (*c* 0.5, pyridine); ^{1}H NMR (C_5D_5N) δ 0.84 (t, 3 H, $J = 6.5$ Hz), 1.10−1.35 (m, 36 H), 1.74−1.98 (m, 4 H), 2.15−2.33 (m, 2 H), 2.35−2.47 (m, 2 H), 2.58−2.74 (m, 2 H), 4.23 (dd, 1 H, $J = 3.5$, 8.0 Hz), 4.27−4.32 (m, 1 H), 4.34 (dd, 1 H, $J = 11.0$, 5.0 Hz), 4.36−4.43 (m, 3 H), 4.48 (dd, 1 H, $J = 6.0$, 6.0 Hz), 4.53 (d, 1 H, $J = 3.0$ Hz), 4.60−4.67 (m, 2 H), 5.23−5.29 (m, 1 H), 5.30−5.80 (br s, 6H), 5.57 (d, 1 H, $J = 3.5$ Hz), 7.14−7.26 (m, 5 H), 8.40 (d, 1 H, J= 9.0 Hz); ^{13}C NMR (C_5D_5N) δ 14.0, 22.7, 26.1, 28.3, 29.4−29.8 (16 C), 31.9, 34.1, 36.3, 36.5, 51.0, 62.4, 68.1, 70.0, 70.8, 71.3, 72.0, 72.8, 76.6, 101.2, 125.7, 128.4 (2 C), 128.6 (2 C), 143.1, 173.0; ESI-MS *m*/*z* = 746.6 $[M + Na]^+$. Anal. Calcd for $C_{41}H_{73}NO_9$ (723.53): C, 68.01; H, 10.16; N, 1.93. Found: C, 68.00; H, 10.17; N, 1.96.

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Supporting Information Available: Experimental procedures and/or characterization data for the synthesis of compounds **3**, **5**−**8**, **10**−**12**, **13a**−**c**, **14a**−**c**, and **17**−**22**, retrosynthetic scheme, Figure 2, ^{1}H NMR spectra of all compounds, and ^{13}C NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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