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A Concise Synthesis of Tetrahydroxy-LCB, α-Galactosyl Ceramide, and 1,4-Dideoxy-1,4-imino-L-ribitol via D-Allosamines as Key Building Blocks

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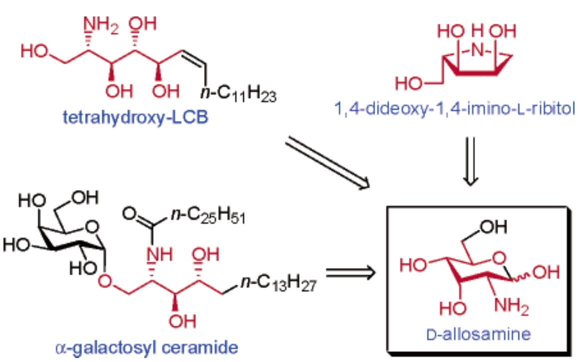

The total syntheses of tetrahydroxy-LCB **1**, α-galactosyl ceramide **2**, and 1,4-dideoxy-1,4-imino-L-ribitol **3** via D-allosamine derivatives as common synthons are described here.

Lipids and glycolipids play significant roles in numerous biological processes.[1] For example, a number of 2-amino-1,3,4,5-tetrahydroxyoctadecene derivatives have been isolated from bovine spinal cords,[2] human brains,[2] and green[3] as well as red algae.[4] Of these, (2*S*,3*S*,4*R*,5*R*,6*Z*)-2-amino-1,3,4,5-tetrahydroxyoctadecene **1**,[5] the long chain base (LCB) part of a new cerebroside was isolated from the latex of *Euphorbia characias L.*, and its structure was elucidated a decade back.[6] α-Galactosyl ceramide (KRN 7000) **2**, a potent analogue of the natural agelasphins isolated from the marine sponge *Agelas mauritianus*,[7] is an important cerebroside exhibiting immunostimulatory activity and antitumor properties. It contains a α-linked D-galactose with phytosphingosine[8]-derived ceramide. Some reports have revealed that **2** is not only a ligand to bind with CD1d molecule and activate natural killer T-cells (NKT cells) to suppress tumor metastases[9] but also a potential agent to prevent autoimmune diseases such as type I diabetes.[10] A few syntheses of **2**[11] and its derivatives[12] have been documented in the literature so far. Recently, a *C*-glycoside analogue of KRN 7000 was synthesized and shown to exhibit remarkably enhanced activity.[13] Iminocyclitols is yet another interesting class of biomolecules. A number of polyhydroxylated piperidines and pyrrolidines, both natural and synthetic, have come up over the past two decades as useful potent glycosidase inhibitors. These are analogues of pyranoses or furanoses with the ring oxygen replaced by an imino group and the anomeric hydroxyl group replaced by hydrogen. Some representatives of iminocyclitols are already marketed as pharmaceuticals and are used in treatment of a certain kind of diabetes, while quite a few others have promising therapeutic potential as antibacterial, anticancer, and antiviral agents.[14] The discovery that certain iminocyclitols inhibit glycoprotein processing and thereby possess anti-HIV activity stimulated interest in this area, and not surprisingly they

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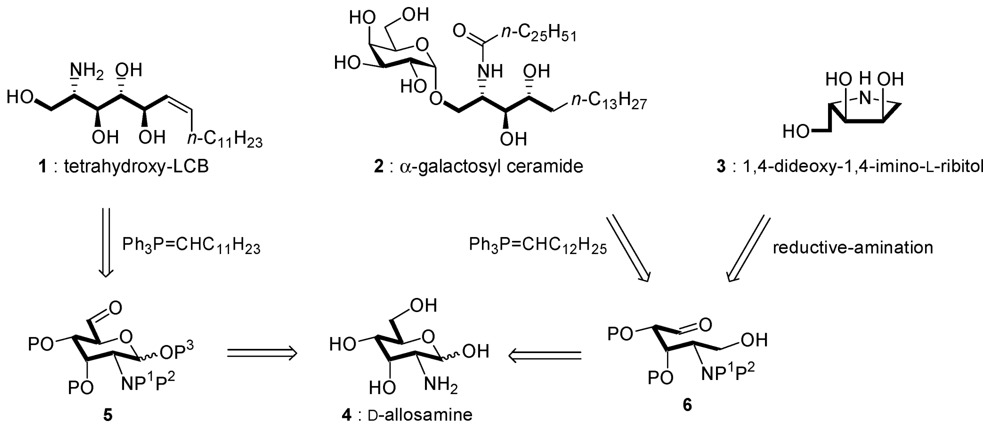
SCHEME 1. Retrosynthetic Plan of Target Molecules 1−3 via D-Allosamines as Common Building Blocks



received a great attention from synthetic chemists.[15] As a part of our ongoing research program to synthesize biologically important lipids, glycolipids, and rare L-form sugars,[16] we report herein a straightforward synthesis of tetrahydroxy-LCB **1**, KRN 7000 **2**, and 1,4-dideoxy-1,4-imino-L-ribitol **3**[17] via D-allosamine derivatives as common synthons.

The common precursor approach demands a careful identification of the similarity between the arrangement of chiral centers in the target molecules and that of the common intermediate. Our retrosynthetic plan, as illustrated in Scheme 1, entails D-allosamine **4** as a common chiral template for the synthesis of **1**, **2**, and **3**; the stereochemical resemblance between compounds **1**−**4** is indicated by the boldfaced carbon framework. It was envisaged that the aldehyde **5**, which can be generated by oxidation of the corresponding semiprotected D-allosamine-derived 6-alcohol, may undergo Wittig olefination followed by deprotection to furnish tetrahydroxy-LCB **1**. On the other hand, the hydroxyl-aldehyde (or hemiacetal) **6**, accessible from the corresponding D-allosamine-derived 1,5,6-triol through oxidative cleavage of the C5−C6 bond, may couple with a Wittig reagent to construct the phytosphingosine skeleton. It can be directly used as the aglycone part in subsequent assembly with an appropriate D-galactose-derived donor to get to the expected target molecule **2**. In addition, reductive amination of the common building block **6** under hydrogenation conditions may provide the final L-form iminocyclitol **3**.

The success of the above synthetic strategy relied on the development of an efficient route to prepare D-allosamine derivatives, amenable to scale-up operations. Some methods have been reviewed in the literatures for their preparations and applications to the total synthesis of naturally occurring allosamidin.[18] To tackle this problem, we have introduced a four-stepped procedure starting from cheaply available D-glucosamine hydrochloride **7**, a C3-epimer of D-allosamine.

Compound **7** was first transformed into the corresponding 1,3-diol **8** through a combination of amino-azido conversion[19] and 4,6-*O*-benzylidenation[20] in 75% overall yield. Differentiation of the free secondary hydroxyl groups in **8** was investigated, and a highly regio- and stereoselective benzoylation, acetylation, and silylation at the O1 position was observed (Table 1). Treatment of **8** with benzoyl chloride in pyridine at 0 °C led to a mixture of 1-OBz, 3-OBz, and 1,3-di-OBz, while use of 1-*N*-benzyloxy-1,2,3-benzotriazole[21] (BzOBT, entry 1) and benzoic anhydride[22] (entry 2) together with triethylamine as a base provided only the β-benzoate **9** ($J_{1,2} = 8.4$ Hz) in 89% and 93% yields, respectively. In entry 3, a similar phenomenon was observed when acetic anhydride was utilized, and the corresponding β-form acetate **10** (92%) was isolated in excellent yield. Although reaction of **8** with *tert*-butyldimethylsilyl chloride and triethylamine (entry 4) failed, employment of imidazole as the base furnished the expected β-silylated product **11**[23] (entry 5, 89%).

The formation of a single β-diastereoisomer in acylation or silylation opens up a more plausible route for C3-epimerization of D-glucosamine into D-allosamine, since the corresponding α-isomer is expected to pose an unfavorable 1,3-diaxial repulsion for the concomitant S_N2 reaction. As outlined in Scheme

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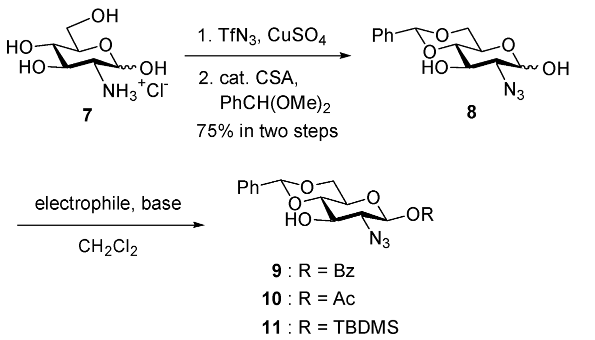
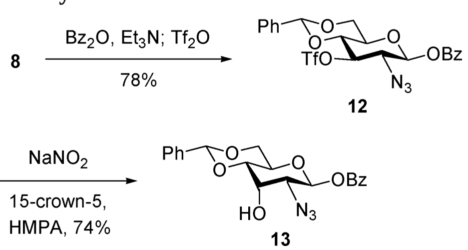
TABLE 1. Regioselective and Stereoselective Protection of D-Glucosamine-Derived 1,3-Diol 8 at the O1 Position



entry	electrophile	base	T (°C)	product	yield (%)
1	BzOBT	Et_3N	rt	**9**	89
2	Bz_2O	Et_3N	rt	**9**	93
3	Ac_2O	Et_3N	rt	**10**	92
4	TBDMSCl	Et_3N	0 to rt	**11**	0
5	TBDMSCl	imidazole	0 to rt	**11**	94

SCHEME 2. Synthesis of D-Allosamine Derivative 13

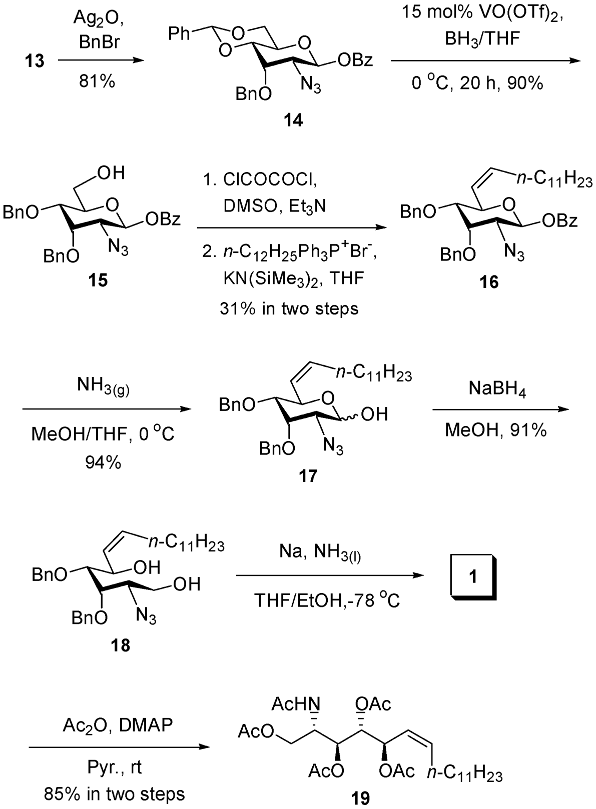


2, O1-benzoylation of compound **8** followed by O3-triflation afforded the corresponding 1-OBz-3-OTf **12** (78%) in a one-pot manner. Nucleophilic substitution of **12** with sodium nitrite in HMPA proceeded well, and the desired C3-epimerized alcohol **13** was obtained in 74% yield. An X-ray single-crystal analysis of **13** was carried out to confirm its absolute configuration (see Supporting Information). Through this efficient and convenient protocol, the D-allosamine derivative **13** was prepared from D-glucosamine in just four steps and in 44% overall yield.

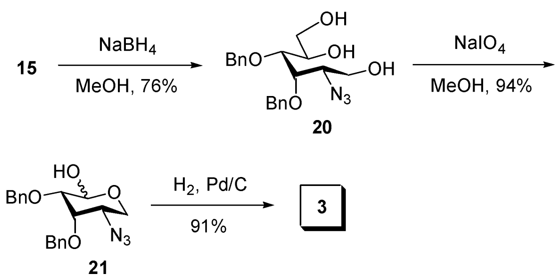
With this potent building block **13** in hand, we further investigated the total synthesis of tetrahydroxy-LCB **1** (Scheme 3). Benzylation of **13** with silver oxide and benzyl bromide yielded the 3-OBn derivative **14** (81%), which was subjected to regioselective ring opening of benzylidene acetal at O6 in the presence of $VO(OTf)_2$ as a catalyst to furnish the primary alcohol **15** in 90% yield.[16g] Oxidation of **15** with PCC provided the corresponding 6-aldehyde, which was not stable during column chromatography purification on silica gel.

Alternatively, Swern oxidation of **15** followed by consecutive Wittig olefination [n-$C_{12}H_{25}Ph_3P^+Br^-$, $KN(SiMe_3)_2$, THF, −78 °C] afforded the requisite *Z*-olefin **16** in two steps in a modest overall yield (31%). The *cis*-stereochemistry of the newly generated double bond of **16** was identified from its ^1H NMR spectrum, which exhibited two distinct downfield signals at δ 5.72 (dt, $J = 10.8$, 7.4 Hz, 1H, H-7) and δ 5.32 (dd, $J = 10.8$, 9.0 Hz, 1H, H-6). Direct reduction of **16** to the 1,5-diol **18** using excess $NaBH_4$ gave disappointing results. Instead, regioselective removal of the anomeric benzoyl group with ammonia led to the corresponding lactol **17** (94%), which was reduced by $NaBH_4$ to get the desired product **18** in excellent yield (91%). Finally, Birch reduction of **18** furnished the target molecule **1**,

SCHEME 3. Synthesis of Tetrahydroxy-LCB



SCHEME 4. Synthesis of 1,4-Dideoxy-1,4-imino-L-ribitol

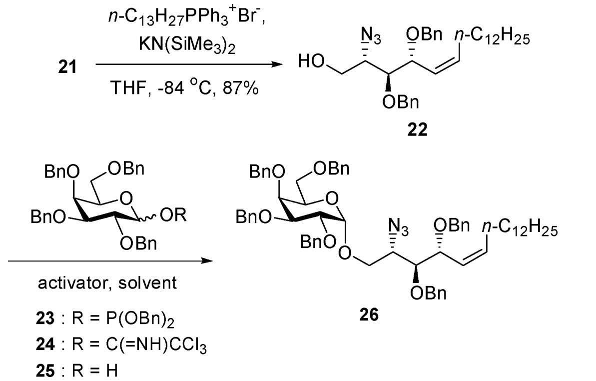


which was characterized as its peracetylated derivative **19** that revealed identity with the literature data[5a] with respect to the ^1H and ^{13}C NMR spectra (see Supporting Information).

Scheme 4 summarizes our synthesis of 1,4-dideoxy-1,4-imino-L-ribitol **3** from the versatile synthon **15** in three straightforward steps. Our strategy is based on the head to tail inversion of **15** followed by preferential *N*-cyclization under hydrogenolytic conditions. In contrast to the hydride reduction of compound **16**, treatment of **15** with $NaBH_4$ in methanol directly led to the triol **20** (76%), which underwent oxidative cleavage with $NaIO_4$ to provide the cyclic hemiacetal **21** in 94% yield. Hydrogenolysis of **21** using palladium on charcoal as a catalyst furnished the final L-form iminocyclitol **3** (91%). The structural identity of compound **3** was confirmed by comparison of its ^1H and ^{13}C spectra with the literature data (see Supporting Information).[17f]

The frequently encountered problems for the preparation of α-galactosyl ceramide **2** include the stereocontrol of α-galactosylation and the generation of the phytosphingosine skeleton with three appropriate chiral centers and a free hydroxyl group at C1 for further coupling. Our approach starting from the

TABLE 2. Coupling of Compound 22 with Various D-Galactopyranosyl Donors To Yield the Product 26



entry	donor	activator	solvent	yield (%)	α/β
1	**23**	TMSOTf	CH_2Cl_2	66	1/1.2
2	**23**	$BF_3 \cdot Et_2O$	CH_2Cl_2	53	1/0.9
3	**24**	TMSOTf	CH_2Cl_2	77	1/1.2
4	**24**	TMSOTf	CH_2Cl_2/dioxane	64	1/1.3
5	**25**	Me_2S, Tf_2O	CH_2Cl_2	73	3.1/1

hemiacetal **21** is described in Table 2. Wittig olefination of compound **21** with $Ph_3P{=}CHC_{12}H_{25}$ at low temperature gave the *Z*-olefin **22** in 87% yield.[8b] It should be noted that several preliminary attempts to effect this reaction under standard conditions met with little success. In situ generation of the phophorane via a slow addition of the base to the well-stirred suspension of **21** and the phosphonium salt at low temperature cleanly afforded the desired product **22**. We then proceeded to study α-galactosylation employing the primary alcohol **22** as an acceptor. Coupling of the dibenzyl phosphite **23** with **22** in the presence of either TMSOTf (entry 1) or $BF_3 \cdot Et_2O$ (entry 2) as an activator did furnish the expected product **26**, in reasonably good yields but as a mixture of anomers in almost equal proportions.[24] TMSOTf-promoted coupling of the trichloroacetimidate **24** was tried next,[25] and compound **26** was obtained with the ratio lying slightly in favor of the unwanted *β*-isomer (entry 3). Inclusion of 1,4-dioxane as a cosolvent in the reaction, with the hope to alter the α/*β* ratio via solvent effect,[26] gave similar results (entry 4). Nevertheless, Gin's sulfide-mediated dehydrative glycosylation[27] using the 1-OH donor **25** offered better yield and selectivity, generating the expected adduct **26** (73%) with the predominance of the α-isomer (entry 5, α/*β*= 3.1/1). While the preparation of this manuscript was in progress, Gervay-Hague and co-workers reported a remarkable stereoselectivity in this glycosylation using glycosyl iodide as donors.[11g] The high selectivity is achieved via in situ anomerization of the α-galactosyl iodide to a more reactive *β*-iodide and its concomitant S_N2 displacement by an electron-rich phytosphingosine acceptor.

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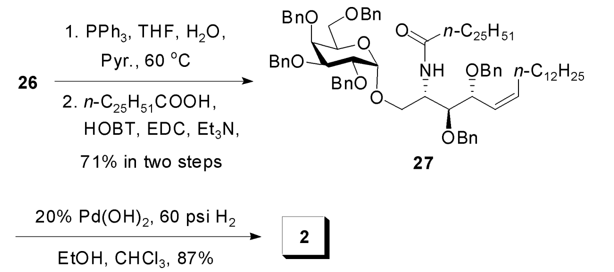
SCHEME 5. Synthesis of α-Galactosyl Ceramide 2



Finally, transformation of compound **26** into α-galactosyl ceramide **2** was carried out in three steps (Scheme 5). Reduction of the azido group in **26** with 3 equiv of PPh_3 in a mixed THF/H_2O (2/1) solvent took a rather extended time (5 d), whereas addition of pyridine in the reaction mixture greatly speeded up the conversion (12 h). The subsequent amide bond formation posed no problems under standard conditions, and the corresponding amide **27** was obtained in 71% overall yield in two steps. Hydrogenolysis of **27** catalyzed by degussa-type reagent under moderate hydrogen pressure (60 psi) led to the final target **2** in excellent yield (87%). The ^1H and ^{13}C NMR spectral data of **2** corroborated well with the literature report (see Supporting Information).[11a]

In conclusion, we have successfully synthesized biologically potent tetrahydroxy-LCB **1**, α-galactosyl ceramide **2**, and 1,4-dideoxy-1,4-imino-L-ribitol **3** using a common precursor approach from D-allosamine. The new strategies described here for their syntheses should provide access to lipid, glycolipid, and iminocyclitol libraries for exploring their immunostimulating activities and other biological properties. The lipid chains can be easily modified, and the stereochemistry can be altered by use of different starting sugars or via epimerization of individual chiral centers.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of all new compounds, spectral comparison for final compounds **2**, **3** and **19**, and X-ray structural information in CIF format for compound **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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