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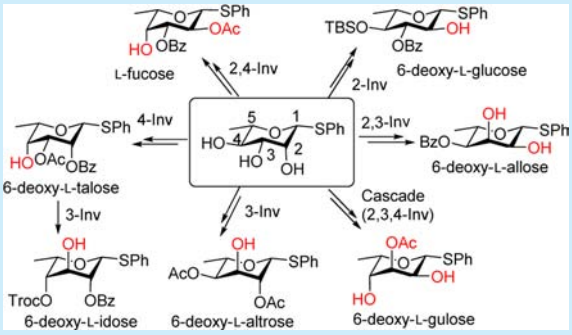
From L-Rhamnose to Rare 6-Deoxy-L-Hexoses

Someswara Rao Sanapala and Suvarn S. Kulkarni*

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai, 400076, India

Supporting Information

ABSTRACT: Efficient and rapid transformation of cheaply available L-rhamnose into all the isomeric 6-deoxy-L-hexoses via regio- and stereoselective nucleophilic displacements of triflates is reported. The synthesis entails regioselective protections, one-pot double displacements of triflates, and cascade inversions. The methodology allows facile access to all the rare 6-deoxy-L-hexoses as stable thioglycoside building blocks.



Rare 6-deoxy-L-hexoses form key components of several biologically important glycopeptides, antibiotics, oligosaccharides, and terpene glycosides.[1] Some representative structures are shown in Figure 1. For example, a 6-deoxy-L-talose-containing repeating disaccharide is found in serotype c of the Gram-negative bacterium *Actinobacillus actinomycetemcomitans*, which is associated with periodontitis and endocarditis.[2] 6-Deoxy-L-talose is also present in talopeptin,[3] and in the glycopeptidolipid antigens of *Mycobacterium avium* serovar 20,[4] as well as O45, O45-related and O66 antigens of *Escherichia coli*.[5] The 6-deoxy-L-glucose (L-quinovose) is present in the O-polysaccharides of the Gram-negative bacteria *Yersinia pseudotuberculosis*[6] and *Providencia stuartii* O44:H4 (strain 3768/51).[7] L-Quinovose is also present in the naturally occurring glycomacrolide Apoptolidin A, which is a potent antitumor agent known to induce apoptosis in cancer cell lines.[8] Zorbamycin, a member of the bleomycin family of glycopeptide-derived antitumor antibiotics, is comprised of a 6-deoxy-L-gulose unit.[9] Likewise, a potent anticancer agent Datiscoside C isolated from the plant *Datiscaglomerata* contains a 6-deoxy-L-allose.[10] 6-Deoxy-L-idose occurs in the diterpene glycoside isolated from *Aster spathulifolius* Maxim.[11] Interestingly, the trisaccharide repeating unit of the pathogen *Yersinia enterocolitica* serovars O:1,2a,3 and O:2a,2b,3 contains 6-deoxy-L-altrose as the sole component.[12] Finally, L-fucose (6-deoxy-L-galactose) is a constituent of many important glycans including Sialyl lewis X (SLex) blood group antigen,[13] whereas L-rhamnose (6-deoxy-L-mannose) is ubiquitous in various bacterial glycans.[14]

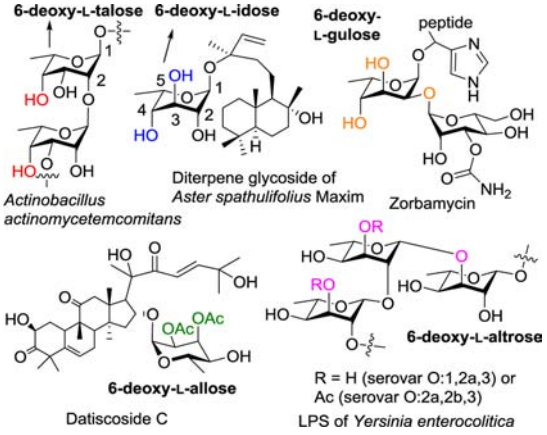


Figure 1. Some examples of 6-deoxy-L-hexoses present in nature.

The 6-deoxy-L-sugars are commercially not available except for L-rhamnose and L-fucose. Numerous methods have been explored for the synthesis of rare 6-deoxy-L-sugars using *de novo* approaches or from readily available sugar starting materials.[15] An attractive *de novo* method has been developed by O'Doherty and co-workers[16] that starts from acetyl furan and uses a Noyori reduction and an Achmatowicz rearrangement as key steps to access 6-deoxy-L-sugars. Recently Bols and co-workers reported the synthesis of all eight stereoisomers of 6-deoxy-L-hexoses as their thioglycoside donors starting from the commercially available L-rhamnose or L-fucose employing stereoselective reductions or Mitsunobu inversions.[17] Although this approach is a marked improvement over the earlier carbohydrate approaches, the development of more convenient routes to synthesize all isomers of 6-deoxy-L-hexoses is still in great demand. We recently established efficient protocols for the synthesis of rare amino deoxy D/L-sugars via one-pot regioselective nucleophilic displacements of triflates.[18] It was envisioned that regio- and stereoselective nucleophilic displacements of suitably tailored triflate derivatives of L-rhamnose would allow expedient access to all the eight isomeric 6-deoxy-L-hexoses. Herein we report a simple, convenient, and straightfor-

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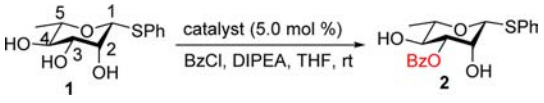
ward transformation of cheaply available L-rhamnose into all the other 6-deoxy-L-sugars as stable thioglycoside building blocks.

Recently, Hale and co-workers revised the Richardson–Hough rules for the S_N2 displacement of pyranosidic triflates.[19] These updates serve as a guiding principle in the designing and planning of new routes for nucleophilic displacements of triflates. Based on the stereoelectronic considerations, β-L-thiorhamnoside **1**[20] was selected as a suitable precursor. First, 3-*O*-benzoylation of **1** was carried out by using 5.0 mol % of various catalysts in DIPEA, benzoyl chloride, and THF to obtain **2** (Table 1). Recently, we reported that the O3-benzoylation of **1**

Table 1. Regioselective Monobenzoylation of β-L-Thiorhamnoside 1 Using Various Catalysts (5.0 mol %)



entry	catalyst	time (h)	yield (%)
1	Me_2SnCl_2	0.17	95
2	2-(trifluoromethyl)phenyl boronic acid	30	78
3	3,5-bis(trifluoromethyl)phenyl boronic acid	30	58[a]
4	$FeCl_3$	30	20[a]
5	copper triflate	5	90

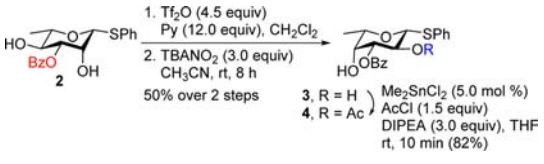
[a]Other isomers were not observed, and unreacted starting material was recovered.

can be achieved by using 5.0 mol % of dimethyl tin dichloride[21] to afford **2** within 10 min at rt in 95% yield (Table 1, entry 1).[18c] Alternatively, we explored various nontoxic catalysts to achieve this transformation under the same reaction conditions. Organoboron species were evaluated next as catalysts for selective benzoylation,[22] and the catalysts 2-(trifluoromethyl)-phenylboronic acid and 3,5-bis(trifluoromethyl)phenylboronic acid provided **2** in 78% and 58% yields, respectively, after stirring for 30 h (entries 2 and 3). Anhydrous $FeCl_3$ (entry 4) as a catalyst, under the same set of reaction conditions, provided **2** in 20% yield. Finally, copper triflate $(Cu(OTf)_2)$[23] was found to be the best readily available, environmentally benign catalyst for this transformation, affording **2** in 5 h in 90% yield (entry 5). However, Me_2SnCl_2 was superior in terms of time and yield.

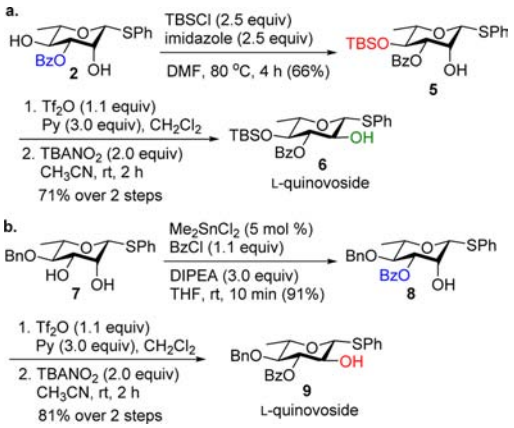
The 2,4-diol **2** upon treatment with triflic anhydride (Tf_2O) and pyridine afforded the corresponding 2,4-bistriflate which underwent a facile double inversion with 4 equiv of tetrabutyl ammonium nitrite ($TBANO_2$) in acetonitrile (Lattrel–Dax reaction)[24] to furnish the L-fucose derivative **3** in 50% yield over two steps (Scheme 1).[18c] The 2-OH of 2,4-diol **3** was regioselectively acetylated using a catalytic amount of Me_2SnCl_2 to obtain selectively protected L-fucoside **4** in 82% yield.

L-Quinovose is a C2 epimer of L-rhamnose (Scheme 2a). For the C2 epimerization, a regioselective silyl protection of L-rhamnosyl diol **2** at the O4 position was carried out by treatment with TBSCl and imidazole in DMF to afford 4-O-TBS derivative

Scheme 1. Direct Transformation of L-Rhamnose into Regioselectively Protected L-Fucose Derivative



Scheme 2. Synthesis of L-Quinovosides 6 and 9

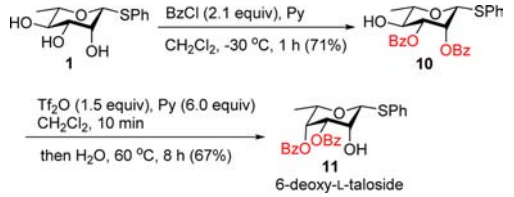


5[18c] as a major product (66%) along with the minor 2-*O*-TBS product (~10%). Subsequent triflation of **5** followed by displacement of the so formed C2-O-triflate with $TBANO_2$ afforded L-quinovoside **6** in 71% yield over two steps.

Similarly, selective 3-*O*-benzoylation of the easily accessible L-rhamnosyl 2,3-diol **7**[20] under tin mediated conditions provided alcohol **8** in 91% yield (Scheme 2b). Subsequent triflation of the 2-OH of **8**, followed by S_N2 displacement of the formed C2-OTf by the nitrite anion, furnished L-quinovoside **9** in 81% yield over two steps.

6-Deoxy-L-talose is a C4 epimer of L-rhamnose. Regioselective 2,3-*O*-benzoylation of L-rhamnoside **1** using 2.1 equiv of benzoyl chloride and pyridine in CH_2Cl_2 at −30 °C afforded 2,3-di-OBz derivative **10** in 71% yield (Scheme 3). Compound **10** was

Scheme 3. Synthesis of 6-Deoxy-L-taloside 11



treated with Tf_2O and pyridine to form the corresponding C4-OTf derivative in 10 min, which was subsequently subjected to a water mediated intramolecular S_N2 displacement of the C4-OTf by the C3-OBz group from the bottom face, to obtain 2-OH L-taloside **11** (67%) via an orthoester intermediate. In this reaction, a double migration of the benzoyl group occurred from C3 to C4 (with inversion of stereochemistry) and concomitant migration from C2 to C3 to give **11**.

The difference between the structures of L-rhamnose and 6-deoxy-L-idose is the stereochemistry at the C3 and C4 positions. Accordingly, a regioselective 3-*O*-acetylation of triol **1** was carried out using Me_2SnCl_2, DIPEA, and acetyl chloride in THF to afford compound **12** in 98% yield (Scheme 4). Regioselective 2-*O*-benzoylation of 2,4-diol **12** under basic conditions by using benzoyl chloride in pyridine at −15 °C furnished compound **13** (92%). Triflation of the remaining free 4-OH of **13** was carried out using Tf_2O in pyridine in 10 min. Upon completion of the reaction, water was added and the reaction mixture was further heated at 50 °C for 3 h to furnish 6-deoxy-L-taloside **14** in 75% yield via intramolecular displacement of triflate by acetate from the bottom face. In this reaction, we obtained 3-OAc L-taloside

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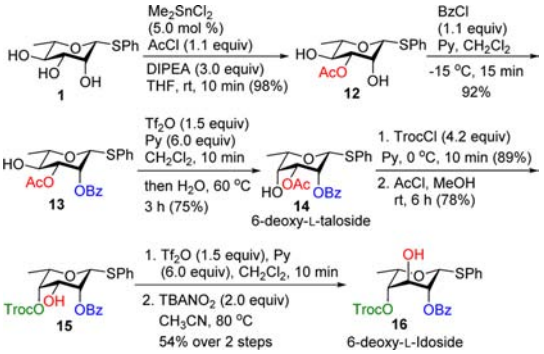
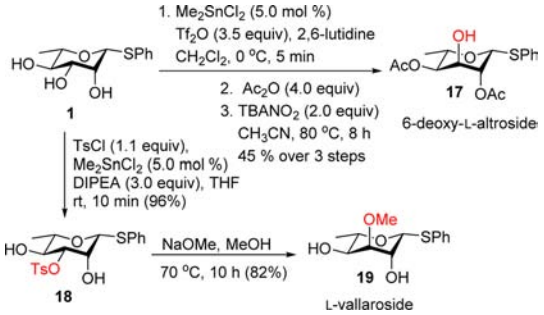
Scheme 4. Synthesis of 6-Deoxy-L-taloside 14 and 6-Deoxy-L-idoside 16 by C2 and C4 Inversion of 1



14 instead of the expected axial 4-OAc L-taloside derivative. It is likely that the first formed C4-OAc would have migrated to the C3 position under the reaction conditions. The 4-OH of **14** was protected as Troc ester, followed by removal of the acetyl group to furnish 3-OH 6-deoxy-L-taloside **15**. Compound **15** upon triflation and subsequent nitrite anion mediated inversion afforded differentially protected 6-deoxy-L-idoside **16** in 54% yield over two steps.

In order to synthesize 6-deoxy-L-altrose, inversion at C3-OH of L-rhamnoside was needed (Scheme 5). Therefore, we

Scheme 5. Synthesis of 6-Deoxy-L-altroside 17 and L-Vallaroside 19 by C3 Inversion of L-Rhamnoside 1



investigated suitable conditions for regioselective 3-*O*-triflation. Under the optimized conditions, a highly regioselective 3-OTf formation of L-rhamnoside **1** was carried out in 5 min using 3.5 equiv of Tf_2O, 5.0 mol % Me_2SnCl_2, and 6.0 equiv of 2,6-lutidine in CH_2Cl_2.[18c] Since the 3-*O*-triflate intermediate was unstable, immediate addition of excess acetic anhydride in the same pot afforded a relatively stable 3-*O*-triflyl-2,4-acetyl-L-rhamnoside derivative, which upon a brief workup was treated with $TBANO_2$ in acetonitrile at 80 °C for 8 h to afford 6-deoxy-L-altroside **17** in 45% over three steps, after a single chromatographic purification.

The rare sugar 6-deoxy-3-*O*-methyl-L-altrose (L-vallarose) is a component of the cardenolides vallaroside and vallarosolanoside which occur in the seeds of *Vallaris solanacea* (Roth) O.K.[25] To date, two routes for the synthesis of L-vallaroside have been reported from 3-*O*-methyl-D-galactofuranoside[26] and by epoxide opening of 2,3-anhydro-*α*-L-rhamnoside.[27] Both approaches involve multiple protecting group sequences and suffer from low yields. For a convenient synthesis of L-vallaroside **19**, regioselective 3-*O*-tosylation of triol **1** was achieved using 5.0 mol % Me_2SnCl_2, 1.1 equiv of tosyl chloride, and DIPEA in THF at rt in 10 min to give a stable tosylate **18** (96%), which upon treatment with sodium methoxide in methanol at 70 °C for 10 h furnished L-vallaroside **19** (82%).

A plausible mechanism for the formation of L-vallaroside **19** is depicted in Figure 2. The transformation from 3-*O*-tosyl

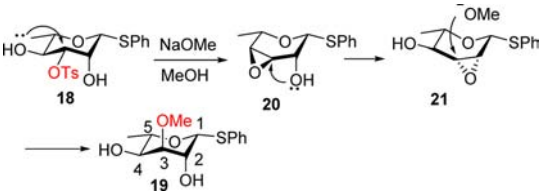
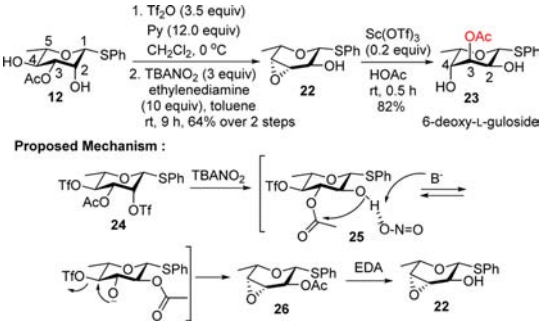


Figure 2. Proposed mechanism for the formation of L-vallaroside.

derivative **18** to L-vallaroside **19** proceeds via tandem oxirane ring opening reactions. Initially, the intramolecular S_N2 attack of C4-OH of **18** from the top face of the ring displaces the C3-tosylate, to form the *exo* 3,4-epoxide **20**, which is further rearranged to the *endo* 2,3-epoxide **21** via intramolecular ring opening of the 3,4-epoxide **20** by the C2-OH. Subsequent opening of 2,3-epoxide **21** by the methoxide anion generated 3-*O*-methyl-L-altroside **19**. Epoxides **20** and **21** were isolated by halting the reaction intermittently and characterized by NMR. KOH in methanol gave similar results.

For the synthesis of 6-deoxy-L-guloside **22**, we needed to carry out inversion at the C2, C3, and C4 positions of L-rhamnose. To achieve this, we opted for the cascade inversion protocol recently demonstrated by Ramström and co-workers on D-gluco and D-galacto scaffolds.[28] First, L-rhamnosyl-2,4-diol **12** was converted to the 2,4-bis-triflate which upon workup was as such treated with 3 equiv of $TBANO_2$ and ethylenediamine (EDA) in toluene to afford 3,4-epoxy alcohol **22** (Scheme 6, 64% over two steps).

Scheme 6. Synthesis of 6-Deoxy-L-guloside 22 via Cascade Inversion and Proposed Mechanism



Treatment of **22** with $Sc(OTf)_2$ in AcOH[16a] furnished 6-deoxy-L-gulose derivative **23** (82%). In this manner, the C2, C3, and C4 stereocenters of L-rhamnoside were inverted via a cascade reaction and subsequent epoxide ring opening.

The proposed mechanism for the formation of **22** is shown in Scheme 6. After the formation of the 2,4-bistriflate **24**, the easily accessible C2-OTf was first displaced by nitrite anion ($^-$O−N=O) to give 4-*O*-triflyl-6-deoxy-L-glucose **25**. The regioselectivity in this case can be attributed to the unfavorable *β*-trans axial effect[19] exerted by the C2-OTf for the incoming nucleophile from the bottom face that discourages attack on C4-OTf. The equatorial C2-OH becomes engaged in hydrogen bonding with the nitrite anion thereby polarizing the O−H bond. This polarization results in the enhancement of acidity of the C2-OH proton which subsequently becomes deprotonated by EDA. A

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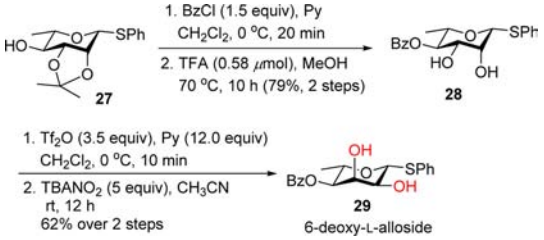
sequential intramolecular attack of the C2-alkoxide onto the carbonyl carbon of the adjacent acetate in **25** leads to acetate migration from C3 to C2. A tandem displacement of the C4- OTf by C3-alkoxide probably results in the formation of a transient 3,4-epoxide **26**, which loses the acetate under the prevailing basic conditions to generate **22**. The cascade reaction is triggered by the nitrite anion through hydrogen bonding with C2-OH as well as a base. No intermediates could be isolated.

Finally, the rare sugar 6-deoxy-L-allose required a C2 and C3 epimerization of L-rhamnose. For this, the known 4-OH L-rhamnoside derivative **27**[20] was treated with benzoyl chloride in pyridine followed by acetal hydrolysis to afford **28** (Scheme 7, 79% over two steps). The 2,3-hydroxyl groups in **28** were subjected to triflation, and subsequent 2,3-bistriflate inversion with $TBANO_2$ provided 6-deoxy-L-alloside **29** in 62% over two steps.

Scheme 7. Synthesis of 6-Deoxy-L-alloside 29 via Vicinal 2,3-*O*-Triflate Inversion of L-Rhamnoside



In conclusion, we have developed a short and efficient method to transform cheaply available L-rhamnose into L-fucose, 6-deoxy-L-talose, L-vallarose, L-quinovose, 6-deoxy-L-gulose, 6-deoxy-L-altrose, 6-deoxy-L-allose, and 6-deoxy-L-idose thioglycosides. The synthesis relies on stereoselective displacements of suitably protected β-L-thiorhamnosyl triflates. In this endeavor, we carried out regioselective protections, regioselective 3-*O*-triflation, cascade inversion, and vicinal triflate displacement to access 6-deoxy-L-hexoses in an expedient manner from L-rhamnose. The stable thioglycoside building blocks of the rare sugars can be further utilized in stereoselective glycosylations for the synthesis of biologically important complex glycoconjugates and natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01796.

Experimental procedures, complete characterization data and copies of ^1H, ^{13}C, and 2D NMR spectra of all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: suvarn@chem.iitb.ac.in.

Notes

The authors declare the following competing financial interest(s): Indian patent application filing is in process. Patent application number 201621022370.

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