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Synthesis of Bicyclo[3.1.0]hexane Derivatives as Conformationally Restricted Analogues of β-Arabinofuranosyl and α-Galactofuranosyl Rings

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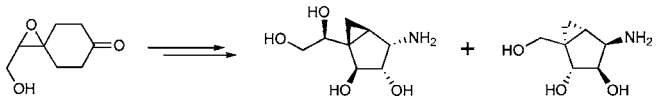
ABSTRACT



A route for the synthesis of bicyclo[3.1.0]hexane-derived conformationally restricted analogues of β-arabinofuranosyl and α-galactofuranosyl rings is described. Advantage is taken of the pseudo-enantiomeric relationship between the two ring systems to develop a route that provides both targets from a single precursor. Key steps include a base-promoted ring contraction of an epoxy ketone obtained from cyclohexane-1,4-dione to give the bicyclo[3.1.0]hexane ring system and a late stage resolution involving esterification with *O*-acetyl-(*S*)-mandelic acid.

Glycoconjugates possessing furanose rings are constituents of organisms ranging from parasites to fungi to bacteria to plants,[1] and increasing attention has been paid to the synthesis of oligofuranosides.[2] We have had a long-standing interest[3] in an arabinogalactan (AG) that is an essential structural polysaccharide of the cell wall in the human pathogen *Mycobacterium tuberculosis* and other mycobacterial species.[4] In the AG, all of the galactose and arabinose residues exist in the furanose ring form. These monosaccharides are absent in humans; therefore, the enzymes involved in AG biosynthesis have attracted attention as targets for novel antibiotics.[5] The knowledge that the clinically used antituberculosis drug ethambutol inhibits the assembly of the AG arabinan domain[6] has further bolstered these efforts.

Arabinogalactan biosynthesis has been studied in some detail, and a number of the enzymes involved in the process have been identified, although not extensively characterized.[7] The assembly of the galactan portion of the molecule is mediated through two bifunctional galactofuranosyltransferases, which use UDP-α-D-galactofuranose (**1**, Figure 1)

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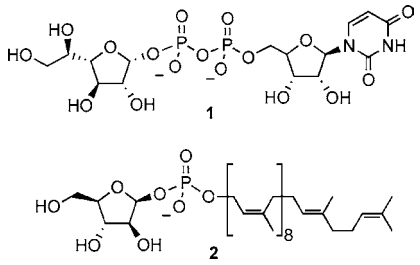

Figure 1. Structures of UDP-α-D-galactofuranose (**1**) and decaprenyl β-D-arabinofuranosyl phosphate (**2**).

as the donor species.[8] The biosynthesis of the arabinan domain is less well understood, but it appears that a number of enzymes, which use decaprenyl β-D-arabinofuranosyl phosphate (**2**) as the donor species, are involved.[4,7,9]

Computational and NMR studies[10] have suggested that **1** and **2** adopt an envelope conformer in which C2 is either above or below the plane formed by the other ring atoms (**3** and **4**, respectively, Figure 2). As part of our continuing

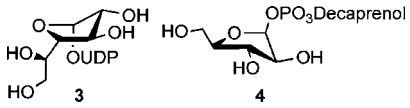

Figure 2. Proposed conformations of UDP-α-D-galactofuranose (**3**) and decaprenyl β-D-arabinofuranosyl phosphate (**4**).

studies on the synthesis of potential inhibitors of mycobacterial arabinofuranosyl- and galactofuranosyltransferases,[3b−e] we wanted to prepare mimetics of **1** and **2** in which the five-membered ring was locked into these conformations. This conformational restriction could be expected to "pre-organize" the molecules for enzyme recognition and thus lead to enhanced affinity. A similar approach has found widespread application in the development of inhibitors of nucleotide-processing enzymes,[11] as well as in the identification of oligonucleotides that bind to their complementary nucleotide sequence with high affinity (e.g., locked nucleic acids[12]).

We therefore selected the bicyclo[3.1.0]hexane derivatives **5** and **6** (Figure 3) as targets. Compounds of this type predict-

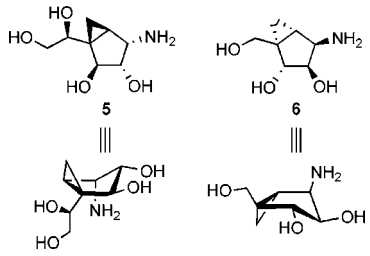

Figure 3. Target molecules **5** and **6**.

ably[11] adopt a conformation in which the cyclopentane carbon forming the flap of the envelope is on the same side of the ring as the cyclopropane methylene group (Figure 3). The amino group was included in the targets for two reasons. First, its presence would facilitate the preparation of additional analogues through, for example, reductive amination. Second, this group would be protonated at physiological pH and thus would be able to form strong ionic interactions with the anionic (carboxylate) groups that are typically present in glycosyltransferase active sites.[13] This charge would also mimic the oxacarbenium ion that develops in the glycosylation transition state.[13]

Compounds **5** and **6** are sterochemically related in that **6** can be obtained from the enantiomer of **5** by oxidative cleavage of the acyclic diol moiety (Figure 4). In this paper,

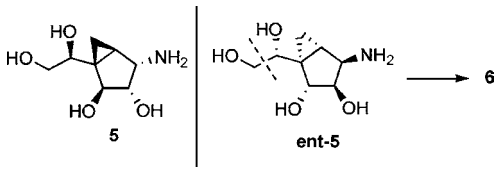

Figure 4. Stereochemical relationship between **5** and **6**.

we describe a synthetic approach to **5** and **6** that takes advantage of this relationship and allows the preparation of the targets in a highly convergent manner from a common intermediate.

The synthesis of the targets started with the known[14] allylic alcohol **7** (Scheme 1). Reaction of **7** with oxalic acid in aqueous acetone led to ketal hydrolysis in 92% yield, thus affording ketone **8**. The hydroxyl group was next protected as a MOM ether under acidic conditions; the product of this reaction, **9**, was obtained in 72% yield. Epoxidation of the alkene with *m*-CPBA afforded a 70% yield of **10**, which was

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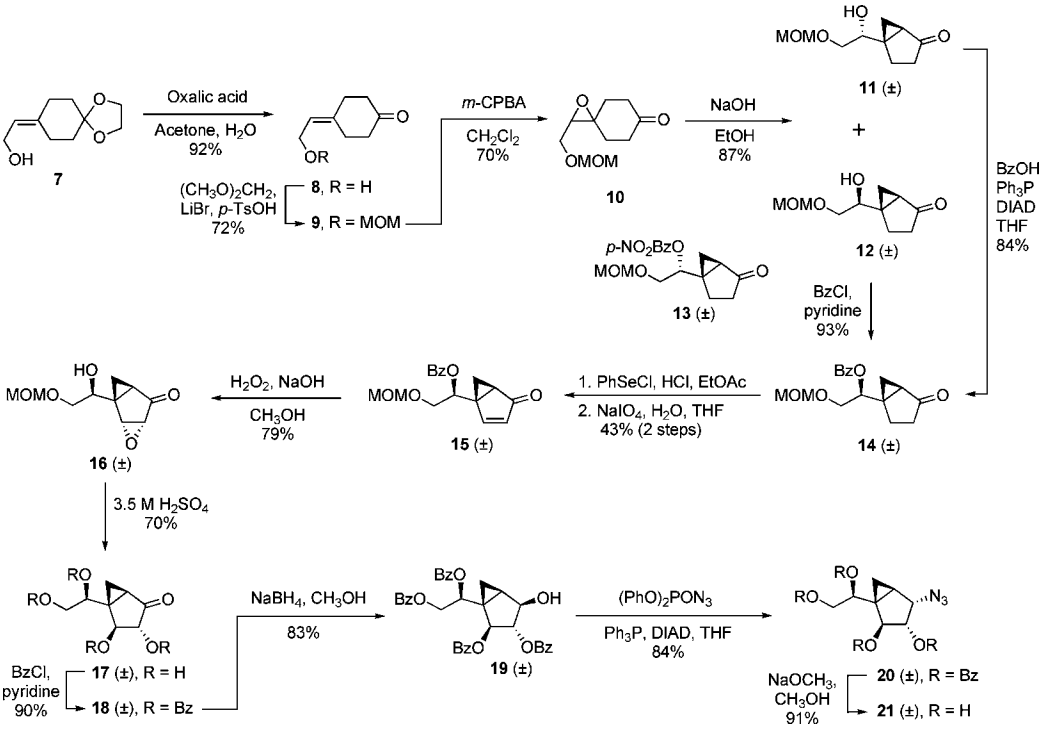
Scheme 1



the substrate for a key ring-contraction reaction. Treatment of **10** with sodium hydroxide in ethanol, as described previously,[15] afforded a ~1:1 mixture of bicyclo[3.1.0]hexane derivatives **11** and **12**, which were readily separable by chromatography. The combined yield of **11** and **12** was 87%.

Determining the relative stereochemistry between the cyclopropane ring and the carbon bearing the hydroxyl group was not possible using NMR spectroscopy. Fortunately, the *p*-nitrobenzoate ester derivative of **11**, compound **13**, was crystalline, and X-ray analysis enabled us to establish[16] the structure of **13** as that shown and, by inference, the structures of **11** and **12**.

With this stereochemical issue addressed, **12** was converted into **14** by reaction with benzoyl chloride and pyridine. The other isomer, **11**, could also be converted into **14** through a Mitsunobu reaction with benzoic acid. In both reactions, yields over 84% were obtained and gram quantities of **14** could be obtained by this sequence.

The protected ketone **14** was then converted into enone **15** in 43% overall yield by α-selenation under acidic conditions, oxidation to the selenoxide, and in situ elimination. In addition to the product, unreacted ketone **14** was recovered. Attempts to improve the yield of this process were unsuccessful; however, **14** and **15** are readily separable by chromatography, and the former can therefore be recycled through the sequence. Reaction of **15** with hydrogen peroxide under basic conditions afforded epoxide **16** in 79% yield. The stereochemistry of this product was established on the basis of NOEs that were present between the oxirane hydrogens and one of the hydrogens present on the cyclopropane methylene group. Finally, the epoxide was hydrolyzed and the MOM group was cleaved upon reaction with aqueous sulfuric acid to give **17** in 70% yield. The regiochemistry of the epoxide opening was apparent from the ^{1}H NMR spectrum of **17**, and a crystal structure of a later intermediate (see below) also confirmed the structure. The regioselectivity of the epoxide opening presumably arises from the partial positive charge that forms during the reaction being stabilized by the cyclopropyl group (i.e., a cyclopropylcarbinyl cation[17]). In addition, formation of the other regioisomer would proceed though a transition state in which this charge develops on the carbon adjacent to the electropositive carbonyl carbon.

Benzoylation of tetrol **17** gave **18**, and treatment of this compound with sodium borohydride reduced the ketone with high stereoselectivity affording **19** in 75% yield over the two steps. The selectivity of the reduction presumably arises from the cyclopropane group, which hinders hydride attack from the top face of the ring. Next, the hydroxyl group was substituted by azide with inversion of configuration in 84% yield via a Mitsunobu reaction with diphenylphosphoryl azide. The fully protected azide **20** was then deprotected upon reaction with sodium methoxide, which afforded **21** in 91% yield.

Having completed the synthesis of **21**, all of the functionality present in the targets was in place and what remained was the resolution of the racemic mixture of products

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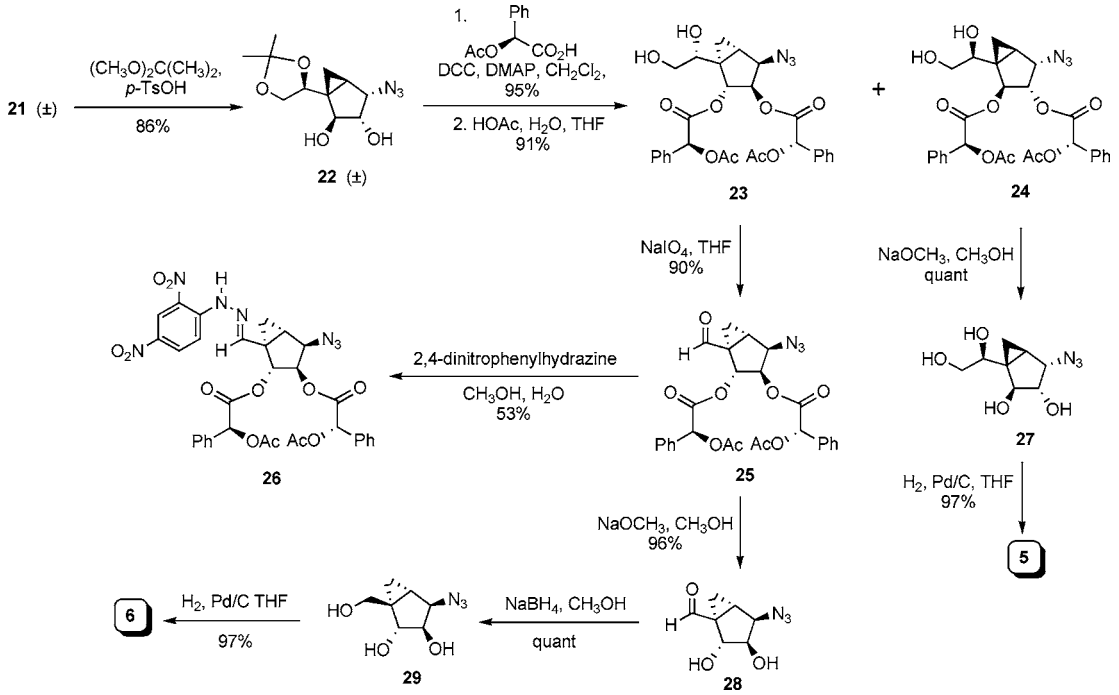
Scheme 2



(Scheme 2). To do this, the acyclic diol in **21** was first protected as an isopropylidene ketal under standard conditions to give the expected product **22** in 86% yield. Esterification of the remaining two hydroxyl groups with *O*-acetyl-(*S*)-mandelic acid led to the formation of an inseparable mixture of diastereomeric products in 95% yield. Removal of the ketal by heating in aqueous acetic acid gave diastereomers **23** and **24**, which could be separated by chromatography, in 91% combined yield.

The structures of **23** and **24** were determined by the preparation of a crystalline derivative of the former. Thus, reaction of **23** with sodium periodate gave aldehyde **25**, which was then converted to the corresponding crystalline 2,4-dinitrophenylhydrazone derivative **26**. Single-crystal X-ray analysis[18] of **26** established the absolute configuration of the molecule as that shown and in turn indicated that **6** could be obtained from **23** and that **24** is the precursor to **5**.

With the absolute configurations of **23** and **24** assigned, the synthesis of the target molecules was completed in a few straightforward steps. The preparation of **5** was carried out by reaction of **24** with sodium methoxide to cleave the mandelate esters (giving **27**) and then reduction of the azide to the amine by hydrogenolysis. Target **5** was obtained in 97% over these two steps. To prepare **6**, aldehyde **25** was deprotected under basic conditions affording a 96% yield of **28**, which was then reduced with sodium borohydride. The product of this reduction, azido-triol **29**, was obtained in quantitative yield. Reaction of **29** with hydrogen and palladium on carbon gave **6** in 97% yield.

In summary, we have described a highly convergent synthesis of conformationally restricted analogues of β-arabinofuranosyl and α-galactofuranosyl rings. A key step is a base-promoted ring contraction of epoxy ketone **10**. A second key feature is a late stage resolution of **21** via partial derivatization with *O*-acetyl-(*S*)-mandelic acid. Enantioselective syntheses of these compounds could be envisaged through the deprotonation of **10** with chiral bases[19] and efforts in that direction are underway. Also ongoing are studies assessing **5** and related *N*-alkylated derivatives as inhibitors of mycobacterial galactofuranosyltransferases.[8,20] It should also be noted that these compounds are new examples of amino-cyclitols (e.g., acarbose and conduramine)[21] and therefore may be glycosidase inhibitors. In this regard, subjecting **24** to the same sequence of reactions reported here for **23** would lead to potential inhibitors of L-arabinofuranosides,[22] which are important in the metabolism of plant polysaccharides.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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