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SYNTHESIS OF STEREOSPECIFICALLY LABELED CARBOHYDRATES II[1]: PREPARATION OF (3*S*)- AND (3*R*)-[3-$^2H_1$]ABEQUOSE

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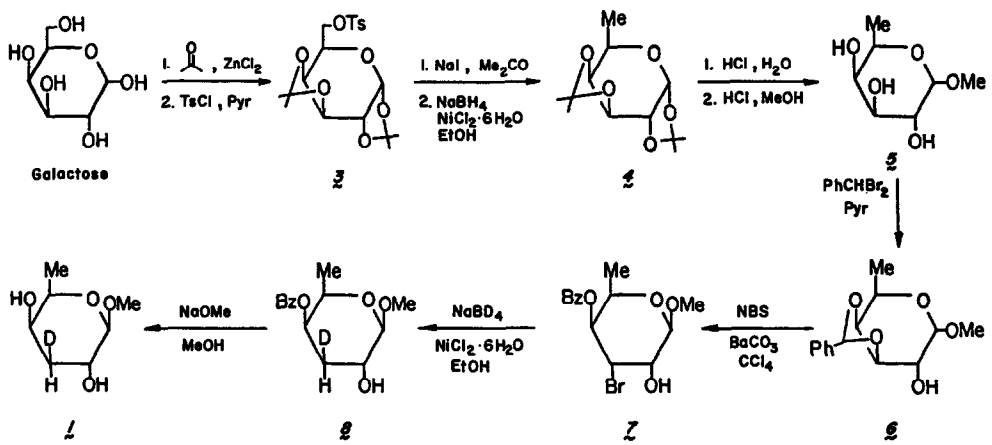
ABSTRACT: Preparation of methyl 3,6-dideoxy-D-*xylo*-hexapyranoside (methyl abequoside) having deuterium stereospecifically labeled at the 3*S* (**1**) and 3*R* (**2**) position, respectively, via three different routes is described.

The 3,6-dideoxyhexoses are found in the lipopolysaccharides of a number of gram-negative bacteria, where they have been shown to be the dominant immunological antigenic determinants.[2] As a part of our continuing efforts to study the biosynthetic formation of 3,6-dideoxyhexoses, it has been necessary for us to develop an efficient and convenient method for the preparation of stereospecifically labeled deoxy sugars.[1] The availability of the sugar derivatives specifically labeled with isotopic hydrogen at the desired loci would allow the enzymatic mechanism and stereochemical course of the associated biosynthetic processes to be examined in detail. In this paper, we wish to report the synthesis of abequose (3,6-dideoxy-D-*xylo*-hexose)[3] stereospecifically labeled with deuterium at C-3 by three routes, all of which are applicable for the preparation of other chirally labeled deoxy sugars.

The first phase of our synthesis called for the construction of a 3-bromo-3-deoxy-hexose ring system possessing the correct stereochemistry on adjacent chiral centers (i.e., **7**). Preparation of this compound, a 3-bromo-3,6-dideoxy-D-*gulo*-hexose derivative, starting with isopropylidenylation of galactose (89%) followed by C-6 tosylation (71%)[4] is summarized in Scheme 1. Deoxygenation at C-6 was accomplished by the treatment of **3** with sodium iodide in a sealed tube[5] and then with sodium borohydride[6] (67%, two steps). Incubation of **3** with Super-Hydride ($LiBHEt_3$, THF, reflux) was a convenient alternative yielding **4** directly (88%). Hydrolysis of **4** followed by methanolysis gave methyl D-fucopyranoside **5** in moderate yield (61%, two steps) as a mixture of α and β stereoisomers. Based on a procedure reported by Eklind et al.,[3d] selective protection of the *cis* diol of **5** with benzylidene bromide and pyridine[7] afforded the 3,4-benzylidene derivative **6** (56%). Upon treatment with N-bromosuccinimide and barium carbonate in carbon tetrachloride, **6** was swiftly converted to the desired 3-bromo-3-deoxyhexose derivative **7** (77%). This regiospecific *trans* ring-opening of benzylidene acetal is well-documented,[8] and the two C-1 epimers became chromatographically discernible at this stage. The β-isomer of **7**, isolated as the major product, adopts a $_4C^1$ conformation which has both the benzoyloxy and bromine groups equatorial. Direct S_N2 displacement of bromine in **7** with various deuteride reducing agents was complicated by decomposition and, in some cases, showed no reaction.

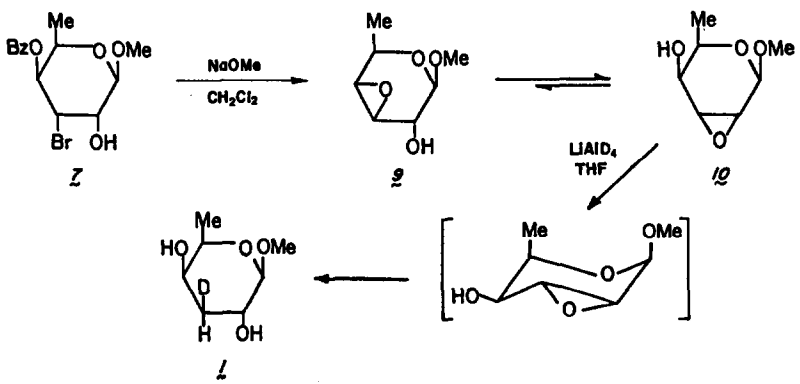
SCHEME 1



The only successful operation in our hands was to employ nickel chloride assisted sodium borohydride reduction in ethanol.[6] The resulting product **8** (66%), upon base hydrolysis, was readily converted to (3*S*)-[3-$^2H_1$]abequose **1**. The corresponding C-1 α isomer of **1** derived from the minor product of **7** can be analogously prepared by the same procedures.

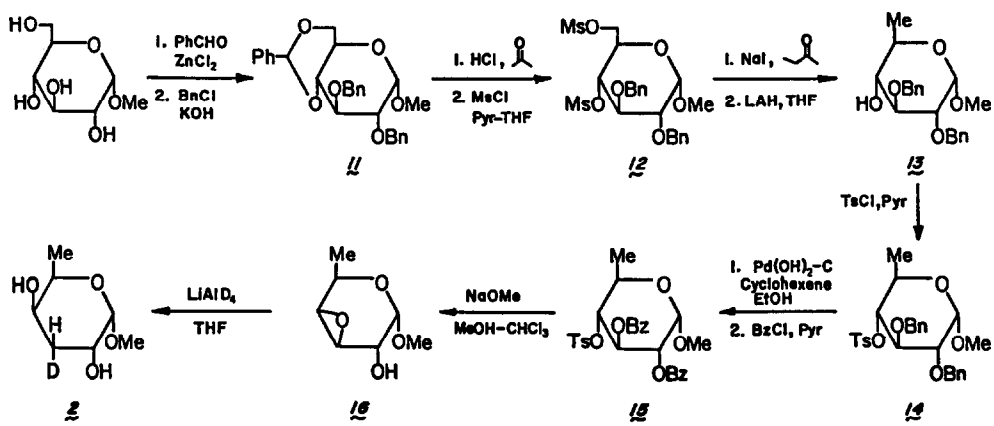
Our strategy to synthesize (3*R*)-[3-$^2H_1$]abequose **2** relied on the preparation of the key intermediate **9**, which upon deuteride reduction should incorporate a deuterium at C-3 with the correct stereochemistry. However, the anhydrogalactoside **9** derived from saponification (NaOMe, CH_2Cl_2) of **7**, having a β substituted C-1 methoxy group, was very unstable due to the propensity of the neighboring C-2 hydroxyl group to participate in the intramolecular opening of the epoxide ring.[9] Despite meticulous control of the

SCHEME 2



reaction temperature and the concentration of the base, compound **9** was readily isomerized to methyl 2,3-anhydro-6-deoxy-β-D-*gulo*-pyranoside **10**. Subsequent reduction with lithium aluminum deuteride of this crude mixture afforded **1** as the major product (75%). The regio- and stereochemical outcomes of this reduction indicated that **10** was the predominant species in this equilibrium which adopted a $_4C^1$ conformation during hydride addition. Nevertheless, this reaction sequence provides a compelling alternative for the preparation of (3*S*)-labeled abequose **1** (Scheme 2). Interconversion by cleavage of the epoxide ring through the vicinal *trans* hydroxyl group is well precedented.[9] Furthermore, it is known that such intramolecular oxide ring opening may proceed only if the adjacent hydroxyl group is axial or pseudoaxial.[10] Examining the molecular model, it became evident that compound **16**, the α epimer of **9**, having its C-2 hydroxyl group in the preferred $^4C_1$ conformation equatorial should be a promising candidate. Preparation of the target molecule **16** starting with methyl glucoside via nine conventional synthetic steps is delineated in Scheme 3. As expected, no epoxide migration from the 3,4- to the 2,3-loci in **16** was found when **15** was treated with base at low temperature (NaOMe, MeOH/$CHCl_3$:1/1, 0 °C), and compound **16** was isolated as the sole product. Reduction of **16** led to axial deuterium incorporation at the pro-*R* position and thus accomplished the synthesis of (3*R*)-[3-$^2H_1$]abequose **2**.

SCHEME 3



To facilitate NMR analysis both compounds **1** and **2** were perbenzoylated. The 300 MHz ^{1}H-NMR of the resulting methyl abequoside perbenzoates were almost identical except for the signals appearing in the region of 1.9-2.6 ppm. The two diastereotopic C-3 methylene hydrogens of the unlabeled species are well resolved as two multiplets at δ 1.97 and 2.57 for the beta isomer and δ 2.27 and 2.43 for the alpha isomer. The disappearance of the high-field signal and the low-field peak in the pro-*S* and the pro-*R* isomer, respectively, provided the key insights for an unambiguous assignment. Namely, the high-field signals can be ascribed to the 3*S* hydrogens and the low-field signals to the 3*R* hydrogens. This information will be extremely useful for the analysis of the stereochemical course of the C-3 deoxygenation step in the biosynthesis of abequose.

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