Tetrahedron Letters,Vol.30,No.42,pp 5729-5732,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF STEREOSPECIFICALLY LABELLED CARBOHYDRATES III[1,2]: PREPARATION OF (3*S*)- AND (3*R*)-[3-$^2H_1$]PARATOSE

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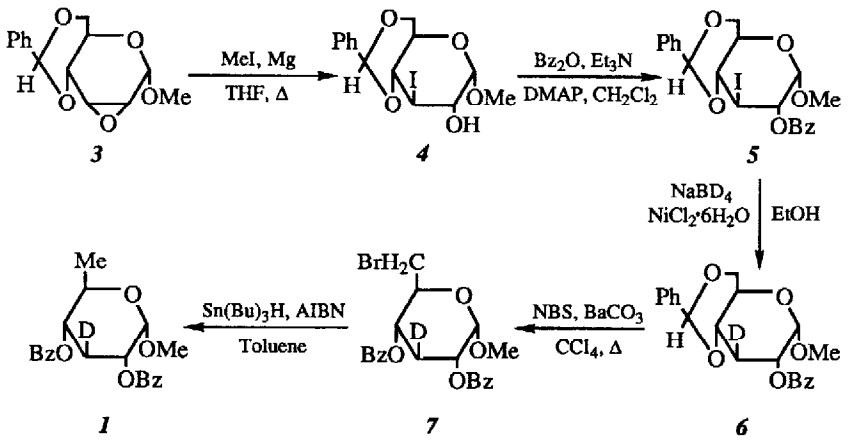
ABSTRACT: Two synthetic pathways producing methyl 3,6-dideoxy-α-D-*ribo*-hexose (methyl paratose) labeled stereospecifically with deuterium at the 3*S* (**1**) and 3*R* (**2**) position, respectively, are described.

The 3,6-dideoxyhexoses exist naturally in the O-specific side chains of cell wall lipopolysaccharides of a number of gram-negative bacteria,[3] where they have been shown to be dominant immunological antigenic determinants.[4] In support of ongoing studies directed toward elucidating a detailed description of the biosynthesis of these sugars, it has been necessary for us to develop a number of chemical synthetic pathways leading to the formation of stereospecifically deuterium labeled versions of these sugars. Earlier articles have discussed the synthesis of stereospecifically labeled ascarylose (3,6-dideoxy-L-*arabino*-hexose)[1] and abequose (3,6-dideoxy-D-*xylo*-hexose).[2] In this paper we wish to report our most recent syntheses, the preparation of (3*S*)- and (3*R*)-[3-$^2H_1$]paratose (3,6-dideoxy-α-D-*ribo*-hexose). Methyl paratose with deuterium incorporated at the C-3 axial position (3*R*) has been previously synthesized by going through a 2,3,4,6-tetra-*O*-(*p*-tolylsulfonyl)-α-D-glucoside intermediate[5] using a procedure which results in an additional deuterium incorporation at C-6. However, the yield from this reaction is very low (16%) and synthesis of the tetra-tosylated intermediate is very time-consuming (it requires 8 days to run to completion). The other isomer (3*S*) has not been previously synthesized.

The first compound to be successfully synthesized was the 3*S* isomer of paratose (see scheme I). It is readily apparent that the crux of this synthesis is the reduction at C-3. Our initial efforts were concentrated on using diisopropylidination to convert glucose to a highly derivatized furanose form. Since this approach conveniently protects all exposed hydroxyl groups except that at C-3, it allows the C-3 hydroxyl moiety to be manipulated by a variety of techniques for deoxygenation as detailed in the literature.[6] Unfortunately, while it was possible to obtain stereospecific reduction at C-3, the inevitable acid catalyzed deprotection removing the isopropylidene groups created a mixture of α and β anomers which complicated further reactions and analyses. We therefore turned our attention to means of manipulating the sugar without recourse to its recalcitrant furanose

form. The first objective of our synthesis was to construct a 3-iodo-3-deoxy-hexose ring system (**5**). This would serve as a convenient stepping stone to 3-deutero-3-deoxy sugars through S_N2 displacement using a deuterated reducing agent. The protected iodosugar was prepared from **3** which was derived from methyl α-D-glucoside in a sequence of benzylidination (78%), ditosylation, and epoxide formation (68%).[7] Iodination of **3** at C-3 was then accomplished through use of the Grignard reagent methylmagnesium iodide in THF at reflux,[8] giving a 78% yield of **4** after an obligatory recrystallization from ethanol. While attack on the epoxide can

SCHEME I

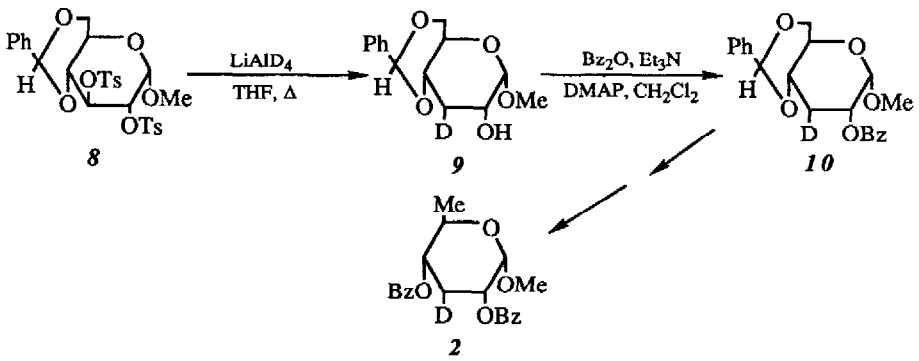


theoretically give four different products resulting from alkyl or halide attack at either of the two carbon atoms involved in the oxide ring, the 3-iodo compound is highly favored under the conditions used. Direct reduction of **4** was attempted but this gave a mixture of compounds due to decomposition and epoxide formation. To avoid this problem, **4** was benzoylated, resulting in **5** which was then reduced in ethanol using sodium borodeuteride and hydrated nickel chloride (94%).[9] Although nickel boride generated in this reaction was reported to be a hydrogenation catalyst rather than a standard metal hydride reducing agent,[10] the stereochemical outcome of this reaction was found to consistently proceed with inversion in work done on other sugar halides.[2,9] Hence, we were quite surprised to note that the deuterium label in **6** had been incorporated at the equatorial position, suggesting that the reduction was occurring with retention, as indicated by the absence of $J_{2,3}$ cis coupling in its NMR spectrum. There are two possible explanations for the unexpected stereochemistry of the product. First, this reduction may actually be a nickel boride catalyzed hydrogenation process, with deuterium being incorporated at the least hindered side. Since iodine removal and deuterium incorporation are both mediated by nickel boride, it is also possible that they may occur in a suprafacial fashion. Second, this reaction may still be a metal hydride mediated reduction since retention of configuration resulting from hydride reduction of an equatorial halide is not without precedent.[6c] In fact, the S_N2 nature of the reduction of alkyl halides - particularly alkyl iodides - has recently been challenged,[11] with a radical mechanism being the proposed successor. Since the reaction course may involve a radical intermediate, the stereochemical outcome is determined by the lifetime and steric hinderance of the radical species, and is no longer confined to inversion as in the direct hydride reduction process. In an attempt to gain further insights of this reduction, compound **5** was

reduced with tri-*n*-butyltin deuteride whose reaction has been well defined as to proceed through a radical mechanism. Interesting, the deuterium labeling pattern of the resulting product was found to be almost the same as that in compound **6**. This finding seems to support a radical mechanism for the conversion from **5** to **6** using $NaBD_4$ and $NiCl_2{\cdot}6H_2O$. Factors controlling the mechanistic diversity of this reduction via either a radical or a hydride pathway are not immediately obvious. A definitive distinction of the reaction mechanism must await a thorough scrutinization of this reduction under well defined conditions. Fortunately, while the isomer obtained was the opposite of that originally expected, we had need of both isomers for our studies so work was continued on from **6**. Upon treatment with N-bromosuccinimide,[12] barium carbonate, and a trace of benzoyl peroxide in carbon tetrachloride, **6** was converted to **7** (57%). Finally, **7** was reduced to **1** using tri-*n*-butyltin hydride[13] and a trace of AIBN in toluene (80%), giving the final product, the dibenzoylated derivative of methyl (3*S*)-[3-$^2H_1$]paratose.

To synthesize the other isomer, methyl (3*R*)-[3-$^2H_1$]paratose, we followed a reaction pathway which was identical in most respects to that used for the synthesis of the 3*S* isomer. However, rather than converting the ditosyl sugar **8** to the epoxide **3**, it was directly reduced using lithium aluminum deuteride in THF.[14] The

SCHEME II



desired compound (**9**) was isolated in 65% yield after recrystallization from ethereal solution with petroleum ether. In this interesting reaction, the 2-*O*-tosyl group of **8** is first cleaved. Lithium aluminum deuteride complexed to the 2-OH formed by this cleavage can then serve as a deuteride donor, displacing the 3-*O*-tosyl group in an S_N2 fashion and resulting in deuterium incorporation in the axial position.[15] Following reduction, **9** was benzoylated to give **10** in quantitative yield. As **10** is identical to **6** except that the deuterium is located in the axial rather than equatorial position, it can be converted to **2** (the dibenzoylated derivative of methyl (3*R*)-[3-$^2H_1$]paratose) using the same reactions that were employed to convert **6** to **1**.

Compounds **1** and **2** were both synthesized as perbenzoylated derivatives in order to facilitate NMR analysis. However, the un-derivatized sugars can be readily obtained through cleavage of the two benzoyl protecting groups.[16] The 300 MHz ^{1}H-NMR of the methyl paratose perbenzoates were essentially identical except for the signals appearing in the 1.8-2.3 ppm region. The two diastereotopic C-3 methylene hydrogens of the unlabeled

species are well resolved as sextets at δ 2.2 and 1.9. The significant reduction of the high-field or low-field signal for the pro-*S* and pro-*R* isomer, respectively, and the simplification of the remaining peak to a triplet in each case, provided unambiguous evidence for the assignments given. This inofrmation will be extremely useful for analyzing the stereochemical course of the C-3 deoxygenation step in the biosynthesis of paratose.

ACKNOWLEDGMENT: Financial support from NIH (GM 35906) is greatly acknowledged. H.W.L. also thanks the Camille & Henry Dreyfus Foundation for a grant awarded to Distinguished New Faculty in Chemistry and the American Cancer Society for a Junior Faculty Research Award.

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(Received in USA 21 July 1989)