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# SYNTHESIS OF STEREOSPECIFICALLY LABELED CARBOHYDRATES: PREPARATION OF (3*S*)- AND (3*R*)-[3-$^{2}H_{1}$]ASCARYLOSE

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ABSTRACT: The general problem of the synthesis of 3,6-dideoxy sugars containing stereospecifically labeled hydrogen isotope at C-3 is addressed for the specific case of ascarylose (3,6-dideoxy-*L-arabino*-hexose).

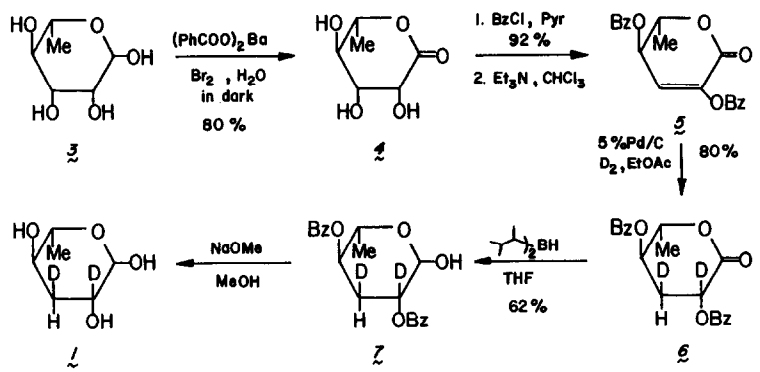
The 3,6-dideoxy hexoses are biologically important carbohydrates which contribute to the serological specificity of many immunologically active lipopolysaccharides.[1] As part of our efforts to investigate the mechanistic and stereochemical course of the biosynthesis of 3,6-dideoxy sugars, it has been necessary for us to prepare the stereospecifically deuterium-labeled 3,6-dideoxy hexoses. Reviewing the literature, we soon discovered not only that the desired labeled sugars were unknown, but that there were very limited examples dealing with the preparation of stereospecifically deuterated sugar molecules. This prompted us to pursue an efficient and practical approach to the synthesis of these labeled hexoses. In this paper, we wish to report the preparation of (3*S*)- and (3*R*)-[3-$^{2}H_{1}$]ascarylose (compounds *1* and *2*, respectively).

As depicted in scheme I, the key intermediate *5* in the synthesis of (3*S*)-[3-$^{2}H_{1}$]ascarylose *1* was prepared from *L*-rhamnose *3* according to the method previously developed by Varela *et al*.[2] Catalytic hydrogenation of *5* with deuterium gas over palladium on carbon stereospecifically introduced the isotopic labels into compound *6*. The stereoselectivity of hydrogenation may be ascribed to the steric hinderance exerted by the *quasi*-axial C-5 methyl group in the $^{0}H_{5}$ conformation of *5* that would prevent the attack of deuterium from underneath the ring.[2,3] Reduction of *6* with disiamylborane in THF followed by debenzoylation with sodium methoxide in methanol furnished the desired 3*S* deuterated ascarylose *1* which is also 2*R* labeled.

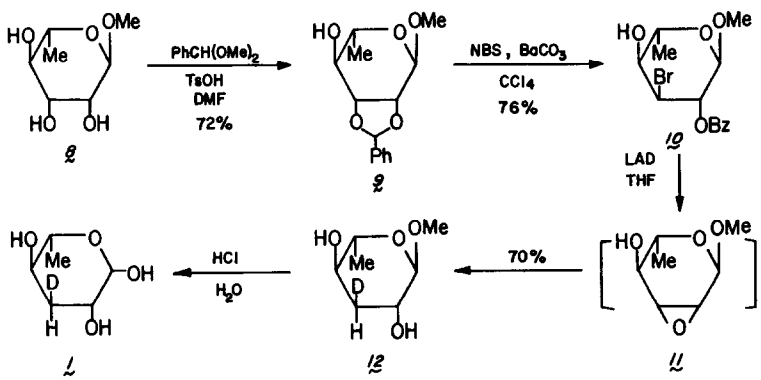
The synthetic scheme reported by Florent *et al*[4] on the synthesis of ascarylose provides an alternative route for the preparation of compound *1*. As shown in scheme II, reaction of 2,3-O-benzylidene *9* with N-bromosuccinimide and barium carbonate in carbon tetrachloride[5] afforded after flash chromatography (10% MeOH/$CH_{2}Cl_{2}$) compound *10* in 76% yield. Subsequent

reduction with lithium aluminum deuteride in THF at reflux temperature led to the incorporation of one deuterium with retention of configuration at C-3. The stereochemical outcome of this reaction implicated the formation of a 2,3-anhydro (epoxide) intermediate *11*. Indeed, treatment of *10* with sodium methoxide in chloroform at room temperature gave the corresponding epoxide *11* which was readily reduced to *12* by lithium aluminum deuteride.[6] Compound *1* was then obtained by acid hydrolysis (0.06 N HCl, reflux) of *12*.

SCHEME I



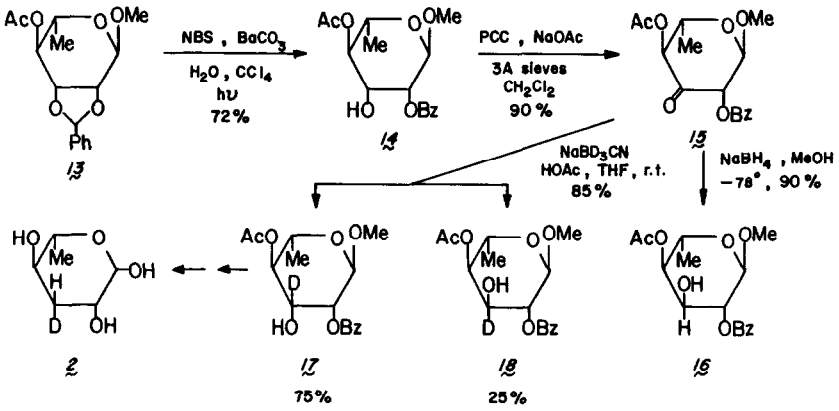

SCHEME II




Preparation of (3*R*)-[3-$^2H_1$]ascarylose *2* was more troublesome. In spite of substantial efforts, we were unable to reduce the bromide in compound *10* directly and/or cleanly under nucleophilic conditions known in the literature to reduce organic halides preferentially.[7] Deoxygenation by boron hydride reagents of the corresponding C-3 tosylhydrazone was also attempted, however, the decomposition of the nascent tosylhydrazine intermediate induced by sodium acetate led to nonstereospecific solvent hydrogen incorporation.[8] Synthesis of *2* was finally accomplished with acceptable yield by the route shown in scheme III. The crucial intermediate *14* was obtained by photolytic cleavage of *13* with N-bromosuccinimide and barium

carbonate.[9] Ring opening of benzylidene acetals by irradiation has been found to be regioselective. The major conformer of the products usually has the benzoyloxy group axial and the hydroxy group equatorial.[10] Upon treatment of *14* with pyridium chlorochromate and sodium acetate in the presence of 3A molecular sieves,[11] compound *15* was obtained in 90% yield. Reduction of *15* with sodium borohydride at -78° gave compound *16* as the only product. However, reduction with sodium cyanoborodeuteride and acetic acid in THF at room temperature produced molecule *17* as the major isomer. Hydrolysis of *17* yielded the desired 3*R* labeled methyl rhamnopyranoside. With (3*R*)-[3-$^2H_1$]rhamnoside in hand, the synthesis of 3*R* labeled ascarylose *2* was swiftly completed by the same reaction sequence (with the exception of lithium aluminum hydride substituted for lithium aluminum deuteride) employed in the second preparation of the 3*S* epimer. To the best of our knowledge, synthesis of C-3 stereospecifically labeled methyl rhamnopyranosides has never been reported. The availability of stereospecifically deuterated rhamnose would allow us to make a wide variety of labeled sugar molecules.

SCHEME III




Both compound *1* and *2* were subjected to methanolysis followed by perbenzoylation, and their NMR spectra were analyzed. The two diastereotopic C-3 methylene hydrogens of the unlabeled methyl ascaryloside perbenzoate were well resolved as two multiplets at δ 2.38 and 2.21 in the 300 MHz $^1$H-NMR spectrum. The high-field signal was drastically diminished in the NMR of compound *1* and the low-field signal, as expected, vanished in the spectrum of compound *2*. Thus, successful preparation of these stereospecifically labeled ascarylose derivatives has allowed an unambiguous assignment of the δ 2.21 and 2.38 signal to the 3*S* and 3*R* hydrogens, respectively. This information will be useful in assessing the overall stereochemistry of the C-3 deoxygenation step in the biosynthesis of ascarylose which is currently being examined.

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REFERENCES AND NOTES:

1. (a) O. Luderitz, A.M. Staub, and O. Westphal, *Bacteriol. Rev.*, *30*, 192 (1966).
(b) N.R. Williams and J.D. Wander, in "The Carbohydrates, Chemistry and Biochemistry", W. Pigman and D. Horton, Ed., Academic Press: New York, 1980, Vol. 1B, p. 761.
2. O.J. Varela, A.F. Cirelli, and R.M. de Lederkremer, *Carbohydr. Res.*, *70*, 27 (1979).
3. R.M. de Lederkremer, M.I. Litter, and L.F. Sala, *Carbohydr. Res.*, *36*, 185 (1974).
4. J-C. Florent, C. Monneret, and Q. Khuong-Huu, *Carbohydr. Res.*, *56*, 301 (1977).
5. S. Hannesian and N.R. Plessas, *J. Org. Chem.*, *34*, 1053 (1969).
6. However, one can not exclude the possibility that reduction may take place on a benzoyl-oxonium cation intermediate produced by the participation of the neighboring benzoyl group at C-2.
7. (a) R.O. Hutchins, C.A. Milewski, and B.E. Maryanoff, *Org. Syn.*, *53*, 107.
(b) R.O. Hutchins, D. Hoke, J. Keogh, and D. Koharski, *Tetrahedron Lett.*, 3495 (1969).
8. (a) R.O. Hutchins, C.A. Milewski, and B.E. Maryanoff, *J. Am. Chem. Soc.*, *95*, 3662 (1973)
(b) V. Nair and A.K. Sinhababu, *J. Org. Chem.*, *43*, 5013 (1978).
(c) D.M. Brown and G.H. Jones, *J. Chem. Soc.*, *(C)*, 252 (1967).
9. R.W. Binkley, *J. Carbohydr. Chem.*, *4*, 227 (1985).
10. R.W. Binkley, G.S. Goewey, and J.C. Johnston, *J. Org. Chem.*, *49*, 992 (1984).
11. (a) J. Herscovici and K. Antonakis, *J.C.S. Chem. Comm.*, 561 (1980).
(b) J. Herscovici, M. Egron, and K. Antonakis, *J.C.S. Perkin I*, 1967 (1982).
(c) S. Czernecki, C. Georgoulis, C.L. Stevens, and K. Vijayakakumaran, *Syn. Comm.*, *16*, 11 (1986).

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