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Synthesis of stereospecifically labeled 3,6-dideoxyhexoses

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ABSTRACT

Preparations of ascarylose (3,6-dideoxy-L-*arabino*-hexose), abequose (3,6-dideoxy-D-*xylo*-hexose), and paratose (3,6-dideoxy-D-*ribo*-hexose) with stereospecific deuterium labeling at C-3 are discussed. The methods used to synthesize these sugars, such as the hydrogenation of olefins, the displacement of halides, the reduction of epoxides, and the substitution of tosyl esters, illustrate a variety of strategies leading to stereospecific deuterium incorporation. Many of the techniques described here should be of general utility for the synthesis of other deuterium-labeled sugars.

INTRODUCTION

The 3,6-dideoxyhexoses exist naturally in the *O*-specific side chains of cell-wall lipopolysaccharides of a number of gram-negative bacteria[1], where they have been shown to be dominant immunological antigenic determinants[2]. Formation of these sugars from 6-deoxy-4-keto-hexoses was found to occur through a complicated series of enzymatic reactions. Previous studies on the biosynthesis of ascarylose (3,6-dideoxy-L-*arabino*-hexopyranose) in *Yersinia pseudotuberculosis* had shown that C-3 deoxygenation in this dideoxy sugar formation is initiated by a pyridoxamine 5′-phosphate-mediated expulsion of the C-3 hydroxyl group, followed by an NADPH-dependent reduction of the resulting 3,4-dideoxy-D-*erythro*-hex-3-enopyranosyl intermediate[3]. The net outcome of these two reactions is the incorporation of a solvent hydrogen at C-3, replacing the original hydroxyl group, to form the 3-deoxy compound. In support of ongoing research directed toward elucidating a detailed mechanism of the biosynthesis of these sugars through the study of enzymes isolated from *Y. pseudotuberculosis*[3a], it has been necessary for us to synthesize several 3,6-dideoxy sugars stereospecifically labeled with deuterium. While a number of methods to synthesize unlabeled versions of these sugars could be found in the literature[2b,4], there was a dearth of information available on carrying out these transformations stereospecifically. Summarized in this paper are our recent efforts in developing methods for the synthesis of stereospecifically labeled ascarylose [3,6-dideoxy-L-*arabino*-hexose (**12**)][5], abequose [3,6-dideoxy-D-*xylo*-hexose (**19**)][6], and paratose [3,6-dideoxy-D-*ribo*-hexose (**24**)]. The paratose and abequose derivatives are to be used as n.m.r. standards in order to

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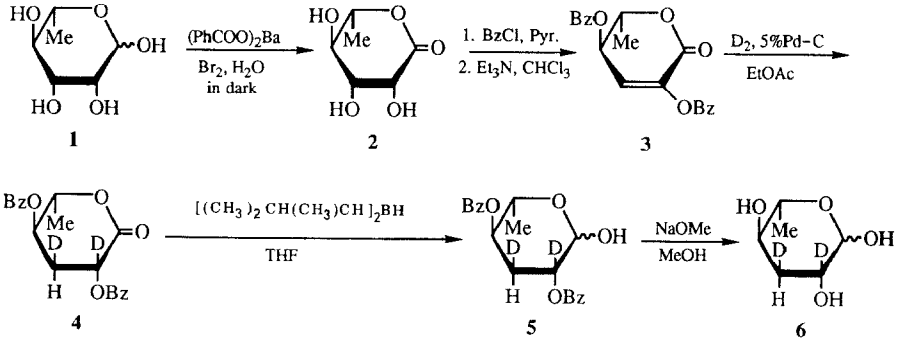
ascertain the stereochemical outcome of the enzymatically controlled deuterium incorporation at C-3, while the ascarylose species (the final product of the biosynthetic pathway) will be used to probe the possible enolization at C-3 during the final steps of the enzymatic pathway. The methods used to prepare these deuterated sugars include the hydrogenation of olefins, displacement of halides, reduction of epoxides, and substitution of tosyl esters. Although some of the results presented have been published in previous communications[5,6], a *vis-a-vis* comparison of the general approaches used and a full account of the experimental procedures involved are described herein for the first time. These results not only detail pathways for the formation of the three sugars named, but also provide useful strategies applicable to the preparation of other stereospecifically labeled carbohydrates.

RESULTS AND DISCUSSION

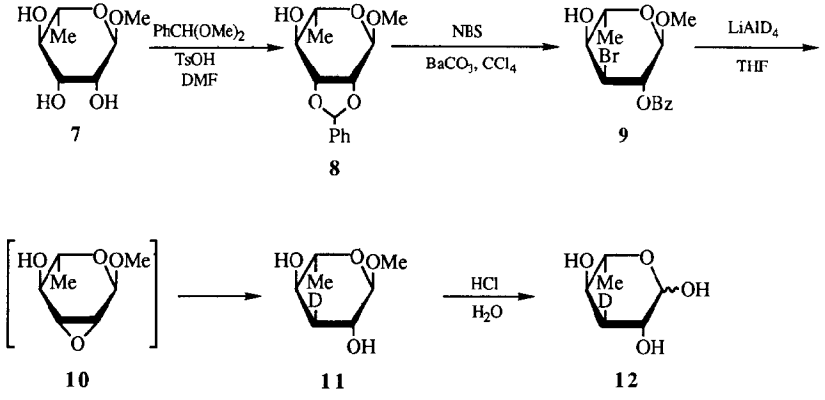
Reduction of olefinic compounds. — Olefins can be used as precursors to synthesize stereospecifically labeled compounds, provided that the inherent steric hindrance around the olefin moiety will impose constraints on hydrogenation sufficient to cause reduction to be directed specifically to the less hindered side of the molecule. This approach was used in our synthesis of (3*S*)-[2,3-$^2H_1$]ascarylose[5] (**6**). The olefinic precursor was synthesized from L-rhamnose (**1**) following the procedure developed by Varela *et al.*[7] As depicted in Scheme 1, L-rhamnose (**1**) was oxidized with bromine to give 6-deoxy-L-mannono-1,5-lactone (**2**). Treatment of **2** with benzoyl chloride and pyridine led to the formation of a perbenzoylated intermediate, which was then converted to 2,4-di-*O*-benzoyl-3,6-dideoxy-L-*erythro*-hex-2-enono-1,5-lactone (**3**) in the presence of triethylamine[8]. Under these conditions, the benzoyloxy group β to the lactone carbonyl was eliminated, and the resulting product **3** was determined to be in the $^0H_5$ conformation by ^{1}H-n.m.r. analysis. Catalytic hydrogenation of **3** with deuterium over a palladium-on-carbon catalyst resulted in stereospecific reduction of the olefin, giving compound **4** in 80% yield. The disappearance of the H-2 peak, the upfield shift of the H-3



Scheme 1.

peak, and the H-3–H-4 spin-spin coupling constant ($J_{3,4}$ 6 Hz) in the ^{1}H-n.m.r. spectrum all support the indicated stereochemical assignment. The stereoselectivity seen in this reaction may be ascribed to the steric hindrance exerted by the *quasi*-axial C-5 methyl group which, in the $^0H_5$ conformation, protrudes from the bottom of the ring structure and prevents attack by deuterium from this direction[7,8]. The synthesis of ascarylose was then completed by reduction of compound **4** with disiamylborane [bis-(3-methyl-2-butyl)borane] in THF[9], followed by debenzoylation with sodium methoxide in methanol. While this scheme represents a rapid (five-step) synthesis of stereospecifically labeled ascarylose, its elegance is partially compromised by the unwanted incorporation of an additional deuterium atom at the 2*R* position. While of minor consequence for our purposes, this sort of double incorporation is the inevitable result of hydrogenation of an olefinic precursor and may limit the utility of this procedure in special cases where the incorporation of only one deuterium atom is desired.

Reduction of anhydro sugars. — Another synthetic strategy useful for the facile preparation of stereospecifically labeled deoxy sugars is to make use of epoxide intermediates. The advantage of using these compounds as precursors for the synthesis of deoxy sugars is that the epoxide ring can be readily opened by a hydride reagent, resulting in a nucleophilic ring cleavage which is usually regio- as well as stereo-specific. Thus, deoxygenation performed on an appropriate substrate by deuteride reagents would introduce the isotope labeling in a well-defined manner. A number of examples using epoxides as intermediates for the synthesis of 2- and 3-deoxy sugars have been described by H. Baer and H. Hanna[4g]. Scheme 2 outlines our preparation of (3*S*) deuterium-labeled ascarylose based on this strategy. Much of this scheme follows the steps developed by Florent *et al.*[10] for the synthesis of unlabeled ascarylose. As shown, the 2,3-*O*-benzylidene derivative **8** was refluxed with *N*-bromosuccinimide in carbon tetrachloride, forming methyl 2-*O*-benzoyl-3-bromo-3,6-dideoxy-α-L-altropyranoside (**9**) in 76% yield. The regiospecific *trans* ring-opening of the benzylidene acetal which oc-



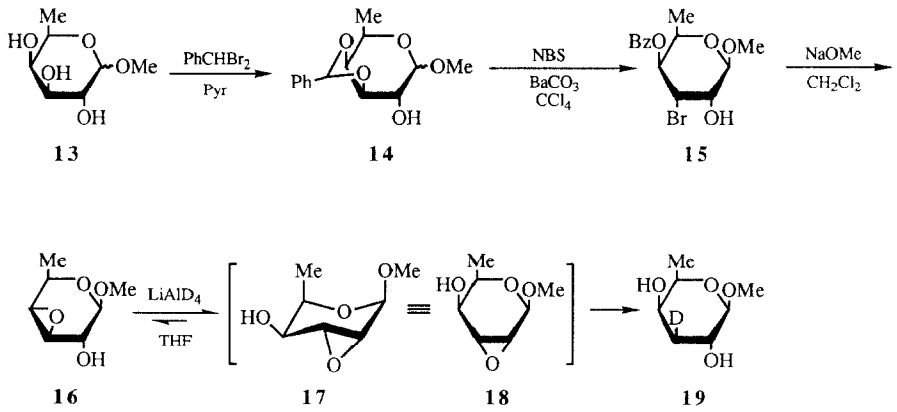
7 8 9

10 11 12

Scheme 2.

curred in this step is well documented[11]. Subsequent reduction with lithium aluminum deuteride in THF at reflux led to the incorporation of a deuterium at C-3 with retention of configuration, as confirmed by the ^{1}H-n.m.r. shift, integration, and coupling values for the hydrogen atom at C-3. If a bromine atom were being directly displaced in this reaction, we would expect to see deuterium incorporation with inversion. Thus, the stereochemical outcome of this dehalogenation may be the result of a double displacement, and the reduction may proceed through a 2,3-anhydro (epoxide) intermediate. Formation of such an epoxide moiety by this route is facilitated by the *trans*-diaxial orientation of the bromo and benzoyl groups and by the highly labile nature of the benzoyl group under reductive conditions. In fact, when **9** was treated with base, the 2,3-anhydro sugar **10** was obtained and could subsequently be reduced to **11** by lithium aluminum deuteride. Thus, while the epoxide shown in this reaction existed solely as a transient species generated during reduction, its usefulness as an effective intermediate was amply demonstrated. The final product, (3*S*)-[3-^{2}H$_1$]ascarylose (**12**), was obtained by hydrolysis of the methyl group at C-1.

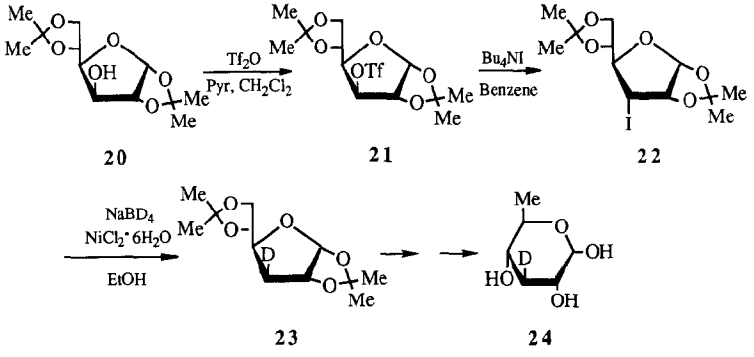
Another example of the use of an epoxide as a deoxy sugar precursor can be found in our synthesis of (3*S*)-[3-^{2}H$_1$]abequose[6] (**19**), as shown in Scheme 3. Compound **13** was prepared from D-galactose as a mixture of α- and β-anomers[6]. The *cis* diol of **13** was selectively protected by benzal bromide in pyridine[12] to give the 3,4-*O*-benzylidene derivative **14**. Upon treatment with *N*-bromosuccinimide in carbon tetrachloride[11], **14** was readily converted to the desired 3-bromo-3-deoxy derivative **15**. The two anomers could be chromatographically separated at this stage, and the β-anomer (shown for **15**) was isolated as the main product. Careful saponification of this compound (NaOMe, CH_2Cl_2, 0°) gave the 3,4-anhydro galactoside **16**. However, the presence of an adjacent free hydroxyl group in a *trans* configuration at C-2 led to a rapid intramolecular epoxide migration upon treatment of this compound with lithium aluminum deuteride. The transient formation of methyl 2,3-anhydro-6-deoxy-β-D-gulopyranoside (**18**) upon re-



Scheme 3.

duction caused the deuterium label to be incorporated at the 3*S* rather than at the 3*R* position, yielding compound **19**. The ^{1}H-n.m.r. spectrum of the latter compound showed one hydrogen atom at C-3 with spin-spin coupling values ($J_{2,3}$ 5.0 Hz and $J_{3,4}$ 3.1 Hz) which are consistent with deuterium incorporation in the axial position. Such an intramolecular migration of the epoxide ring through the vicinal *trans* hydroxyl group in an axial or pseudoaxial orientation is well precedented[13] and must be taken into account when designing a synthetic scheme of this type. The regio- and stereo-chemical outcomes of this reduction suggested that compound **18** adopted a $^1C_4$ conformation (**17**) during deuteride addition. However, when the *α*-epimer of **16** was used, (3*R*)-[3-^{2}H$_1$]abequose could be obtained in high yield upon reduction with lithium aluminum deuteride[6]. Since the *α*-epimer of **16** assumes a $^4C_1$ conformation, the C-2 hydroxyl group is in an equatorial position and is thus unable to participate in intramolecular epoxide ring opening[14].

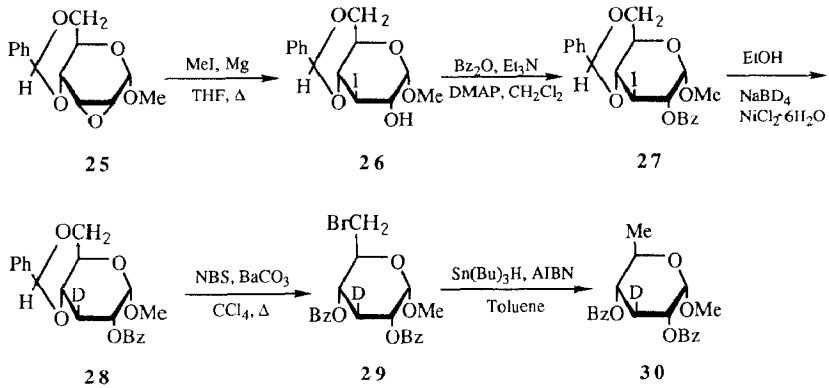
Reduction of sugar halides. — One of the most common ways of synthesizing deoxy sugars is through the reduction of deoxyhalogeno intermediates[15]. For C-3 deoxygenation, a convenient approach starts with the preparation of 1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose[16] (**20**) which is highly stable and has a readily accessible hydroxyl group at C-3 available for chemical manipulation. In our initial attempts to synthesize stereospecifically labeled paratose (Scheme 4), **20** was prepared and treated with trifluoromethanesulfonic anhydride and pyridine in chilled dichloromethane, affording the trifluoromethanesulfonate **21** in quantitative yield. The trifluoromethanesulfonate (triflate) was then treated under reflux with tetrabutylammonium iodide in benzene to give the deoxyiodo sugar[17] **22**. Upon reduction of **22** by sodium borodeuteride and nickel chloride in ethanol[18], the [3-^{2}H$_1$]glucofuranose derivative **23** was formed with inversion of configuration at C-3. The ^{1}H-n.m.r. chemical shift (2.15 p.p.m.) and coupling constant ($J_{3,4}$ 3.6 Hz) confirmed this assignment. Selective deprotection of the 5,6-*O*-isopropylidene group[19], followed by C-6 deoxygenation and acid hydrolysis, led to the desired paratose with deuterium labeling at C-3. This approach is rather straightforward and may be the method of choice to prepare a C-3



20 21 22

23 24

Scheme 4.



Scheme 5.

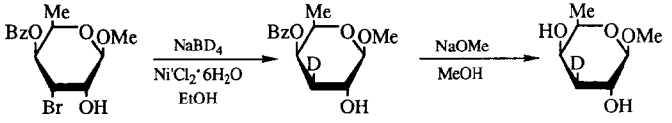
labeled reducing sugar. Although the corresponding methyl glycoside could be directly prepared by methanolysis of the 1,2-*O*-isopropylidene protecting group, the product thus obtained was always found to be a mixture of *α*- and *β*-anomers, which are often difficult to resolve and thus complicate further reactions and analyses.

Another scheme which we used to prepare methyl (3*S*)-[3-$^2H_1$]paratoside again made use of a deoxyhalogeno intermediate, as shown in Scheme 5. The new scheme avoided the furanose form and its associated anomerization problems by retaining the pyranose ring system throughout the synthesis. After forming methyl 2,3-anhydro-4,6-*O*-benzylidene-*α*-D-allopyranoside[20] (**25**), iodination at C-3 was accomplished through the use of the Grignard reagent, methylmagnesium iodide, in THF at reflux[21]. Attack on the epoxide under these conditions can theoretically give four different products, resulting from alkyl carbanion or halide attack at either of the two epoxide carbon atoms[21]. Fortunately, formation of the desired 3-iodo compound **26** is highly favored under the conditions used, and it was isolated in 78% yield. Direct hydride reduction of **26** was attempted, but the 3-deoxy sugar product was heavily contaminated by the 2-deoxy sugar resulting from concurrent reduction of the 2,3-anhydro sugar **25** that was also formed from **26** under these conditions. To circumvent this problem, **26** was benzoylated to prevent epoxide formation, yielding **27** in quantitative yield. Compound **27** was then reduced in ethanol with sodium borodeuteride and hydrated nickel chloride[18] to give a 94% yield of **28**. ^{1}H-n.m.r. analysis of the product showed that the deuterium label at C-3 in **28** had been incorporated at the equatorial position, since no *cis* H-2–H-3 coupling was discernible. As described earlier, when this reducing reagent was used on the furanose compound **22** with iodine at C-3, the reduction proceeded normally with inversion. However, when iodine was present at the equatorial position of a pyranose ring as it was in compound **27**, reduction clearly occurred with retention. The same result was obtained when sugar **27** was protected at the C-2 position with a *β*-methoxyethoxymethyl ether group[22] in place of the benzoyl ester group. Although the determining factors governing this unusual stereoselectivity are not immediately apparent, it is unlikely that the chemical nature of the adjacent protecting group plays any role

in controlling the stereochemistry of the reduction. While this unexpected result may be ascribed to catalysis by nickel boride generated *in situ* that serves as a hydrogenation catalyst, rather than a standard metal hydride reducing agent[23], retention at C-3 upon reduction has also been reported when lithium aluminum hydride was used to reduce 3-chloro-3-deoxy-1,2:5,6-di-*O*-isopropylidene-*α*-D-*ribo*-hexofuranose[4e]. Since retention of configuration has been found in reductions by different metal hydride reducing agents, these results obviate the need to postulate a nickel boride-mediated hydrogenation as the only explanation for the observed stereochemical outcome. An alternate, and perhaps a more likely, explanation for this unusual result can be found in the recent work of Ashby *et al.*[24], who have demonstrated that the metal-hydride reduction of alkyl halides, especially alkyl iodides, appears to go through a free-radical rather than an S_N2 mechanism. Interestingly, when compound **27** was reduced with tributyltin deuteride, which is a well-known free-radical reducing agent, the labeling pattern at C-3 of the resulting product was identical to that of compound **28**. This result seems to support a free-radical mechanism for the conversion of compounds **27** to **28** mediated by $NaBD_4$/$NiCl_2 \cdot 6H_2O$ and should be a useful adjunct to other studies of metal-hydride reactions and their possible recourse to radical mechanisms during the reduction of halides. A definitive distinction of the reaction mechanism must await a thorough scrutiny of this reduction under well-defined conditions. Following reduction, compound **28** was brominated using *N*-bromosuccinimide in carbon tetrachloride at reflux[11] to give **29**, which was then reduced using tributyltin hydride in toluene[15h] to give the perbenzoylated derivative of (3*S*)-[3-$^2H_1$]paratose (**30**).

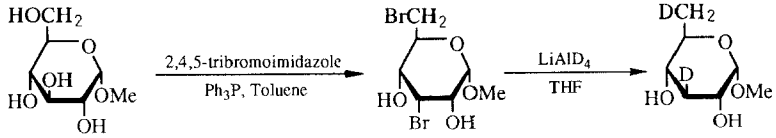
Another application of this strategy is exemplified by our synthesis of (3*S*)-deuterated abequose. This synthesis uses an intermediate **25** common to that of an epoxide pathway already discussed, and it is shown in Scheme 6. When the 3-bromo-3,6-dideoxy-D-gulopyranoside derivative **15** was treated with sodium borodeuteride and nickel chloride in ethanol[18], reduction occurred normally with inversion, giving the (3*S*)-[3-$^2H_1$] isomer of abequose **19** after saponification of **31**. The ^{1}H-n.m.r. spectrum for this compound possessed the same stereochemistry as **19** (described earlier), with the exception that the benzoyl group at C-4 caused the adjacent proton to be shifted further downfield. This is the same product that was earlier obtained through an epoxide intermediate, but, as the benzoyl group is stable under the milder reduction conditions used here, an epoxide intermediate was not generated.

The final example from our syntheses of the stereospecific reduction of deoxyha-



15 31 19

Scheme 6.



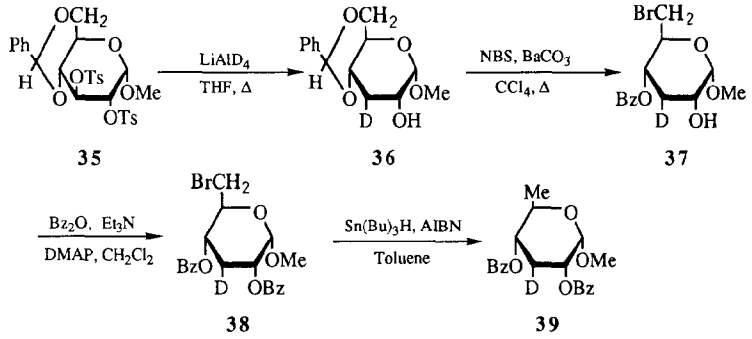
32 33 34

Scheme 7.

logeno sugars is one of special utility with regards to paratose synthesis, in that it makes use of a dibrominated precursor possessing bromine at both the C-3 and C-6 positions. This compound **33** was prepared from methyl α-D-glucopyranoside (**32**) using 2,4,5-tribromoimidazole and triphenyl phosphine in refluxing toluene[25]. Subsequent reduction proceeded normally with inversion, allowing (3*S*)-[3,6-$^2H_2$]paratose (**34**) to be synthesized in only two steps overall, as shown in Scheme 7. While halogenation at C-6 proceeds in a relatively straightforward fashion, the mechanism for the selective halogenation at C-3 has not yet been fully characterized. The C-3 position of methyl α-D-glucopyranoside (**32**) usually shows little reactivity toward nucleophilic substitution due to steric interference from a 1,3-diaxial interaction between the α-methoxyl group and the incoming nucleophile[15e,25,26]. Classon *et al.*[25] have speculated that inversion of the normal $^4C_1$ conformation of **32** to a $^1C_4$ conformation, facilitated by the elevated temperature and trapped by a cyclic phosphonium diester bridging between O-2 and O-4, might avoid this problem, leaving the hydroxyl group at C-3 free to be halogenated. Following the formation of methyl 3,6-dibromo-3,6-dideoxy-α-D-allopyranoside (**33**), reduction with lithium aluminum deuteride yielded compound **34**. The double deuterium incorporation was confirmed by the upfield shift of the hydrogen atoms at C-3 and C-6, while the exact site of incorporation at C-3 was shown to be equatorial by the coupling values ($J_{2,3} = J_{3,4} = 11.5$ Hz). If one wishes to avoid deuterium incorporation at C-6, a milder reduction using lithium aluminum hydride (THF, room temperature) can be used to selectively reduce the C-6 bromo group prior to deuteride reduction of the C-3 bromo group under harsher conditions (THF, reflux).

Reduction of tosylated sugars. — Another method that we found useful for the synthesis of stereospecifically labeled sugars made use of tosylated sugars which could be subsequently reduced (reductive detosylation) to yield deoxy sugars. Tosyl ester groups are similar to halides in that they are good leaving groups and can be readily displaced by nucleophiles. However, unlike halides, they can also be reduced directly at the sulfur center (desulfonyloxylation) to regenerate the original hydroxyl moiety, releasing toluenesulfinate as the by-product. This was indeed found during the reduction of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolylsulfonyl)-α-D-glucofuranose with lithium triethylborohydride in which compound **20** was isolated as the only product[4g]. Since the sulfonyl ester itself (O–S fission) and the substituted carbon (O–C fission) are both susceptible to hydride attack, reduction of sugar tosylates is somewhat more complicated than that of sugar halides. One example making use of a tosylated sugar can be seen in Scheme 8, which shows the preparation of methyl (3*R*)-[3-$^2H_1$]paratoside starting from the ditosylated sugar[20] **35**. Upon reduction by lithium aluminum deuteride in THF at

reflux[27], the desired deoxy sugar **36** was isolated in 65% yield after recrystallization. The axial position of the incorporated deuterium atom was confirmed by the ^{1}H-n.m.r. spectrum ($J_{2,3} = J_{3,4} = 4.5$ Hz). In this interesting reaction, the 2-*O*-tosyl group is rapidly cleaved by lithium aluminum deuteride[4g,28]. The resulting alkoxyaluminum deuteride complex (R–O–AlD_3–) that incorporated the C-2 hydroxyl group can then serve as a deuteride donor, displacing the C-3 tosyl group in an S_N2 fashion, resulting in deuterium incorporation in the axial position[29]. Following this reduction, compound **36** was brominated with *N*-bromosuccinimide to give compound **37**, which was then treated with benzoic anhydride and reduced using tin hydride, yielding perbenzoylated paratose **39**. The benzoyl groups were incorporated to facilitate ^{1}H-n.m.r. peak differentiation, and these could be removed by saponification.



35 36 37 38 39

Scheme 8.

The syntheses described in this report should provide convenient procedures for the fabrication of stereospecifically labeled ascarylose, abequose, and paratose. In addition, these methods should be of general utility for the preparation of other deoxy sugars.

EXPERIMENTAL

General. — Melting points were determined with a Mel-Temp apparatus and are uncorrected. Mass spectra were obtained with a VG 7070E-HF spectrometer. ^{1}H- and ^{13}C-n.m.r. spectra were recorded with an IBM NR/200 or NR/300 spectrometer. Chemical shifts are reported in p.p.m. on the δ scale relative to internal standard (tetramethylsilane or appropriate solvent peaks) with coupling constants given in Hz. N.m.r. assignments labeled with an * may be interchangeable. Flash chromatography was performed in columns of various diameters with J. T. Baker (230–400 mesh A.S.T.M.) silica gel by elution with the solvents reported. Analytical thin-layer chromatography (t.l.c.) was carried out on Merck Silica Gel-60 GF-254 plates (25mm) and developed with the solvents mentioned. T.l.c. spots were visualized either with u.v. light or by dipping the plates into staining solutions of 1:98:1 vanillin–ethanol–H_2SO_4 or phosphomolybdic acid (7% EtOH solution) and then heating them. Solvents, unless

otherwise specified, were reagent grade and distilled once prior to use.

*6-Deoxy-*L*-mannono-1,5-lactone* (**2**). — Bromine (1 g, 6.2 mmol) was added to an ice-cold solution of L-rhamnose monohydrate (**1**) (9.1 g, 55.5 mmol) and barium benzoate (30 g, 81 mmol) in water (375 mL). The reaction mixture was stirred with a mechanical stirrer for 48 h at room temperature in the dark. Excessive bromine was removed by bubbling air into the solution, and the barium species was precipitated by adding 5N sulfuric acid (26 mL). Charcoal was added and barium sulfate was filtered off. Lead carbonate (13.5 g, 17.4 mmol) was then added to neutralize excessive hydrobromic acid, and the lead salts were removed as lead sulfide by bubbling H_2S through the solution and filtering off the resulting precipitates. The filtrate was concentrated, and any residual benzoic acid was removed by extracting the concentrated aqueous solution several times with chloroform. The aqueous solution was neutralized with calcium carbonate and then concentrated to 30 mL. The crude product was isolated as a solid, and pure lactone **2** (7.2 g, 80%) was obtained by recrystallization from ethanol: m.p. 163° (lit. [30]m.p. 165°).

*2,4-Di-*O*-benzoyl-3,6-dideoxy-*L-erythro-*hex-2-enono-1,5-lactone* (**3**). — Compound **2** (0.91 g, 5.6 mmol) was suspended in dry pyridine (25 mL), and to this solution was slowly added, under nitrogen, distilled benzoyl chloride (3.03 g, 21.6 mmol). The reaction was stirred for 16 h at room temperature. The excess pyridine was removed *in vacuo*, and the product was purified by flash chromatography (11:19 EtOAc–benzene). The purified perbenzoylated lactone product (2.06 g, 4 mmol) was dissolved in 1:4 triethylamine–chloroform (100 mL) and stirred under nitrogen for 16 h. The reaction mixture was then extracted with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude enone product was purified by flash chromatography (benzene) to give compound **3** (1.48 g, 75%): m.p. 107–110° (lit.[7] m.p. 108–110°). ^{1}H-n.m.r. data ($CDCl_3$): δ 8.15–7.45 (10 H, m, ArHs), 6.72 (1 H, d, J 5.0 Hz, H-3), 5.70 (1 H, dd, J 5.0 and 5.0 Hz, H-4), 5.05–4.90 (1 H, m, H-5), and 1.65 (3 H, d, J 7.0 Hz, 5-Me).

*(3*S*)-[2,3-$^2H_2$]-2,4-Di-*O*-benzoyl-3,6-dideoxy-*L*-mannono-1,5-lactone* (**4**). — A solution of compound **3** (500 mg, 1.4 mmole) was reduced with deuterium over 5% Pd–C (50 mg) in ethyl acetate (35 mL) at 0°. After the reduction was complete, the reaction mixture was filtered, and the filtrate was concentrated to give the crude product. Compound **4** was purified by recrystallization from ethanol to give pure **4** (405 mg, 80%): m.p. 83° (lit.[7] m.p. 85–87°). ^{1}H-n.m.r. data ($CDCl_3$): δ 8.15–7.40 (10 H, m, Ar Hs), 5.90 (0.5 H, d, J 11.0 Hz, H-2), 5.28 (1 H, dd, J 6.0 Hz, 6.0, H-4), 4.82 (1 H, m, H-5), 2.70 (1 H, m, H-3), and 1.60 (3 H, d, J 6.0 Hz, 5-Me).

*(3*S*)-[2,3-$^2H_2$]-2,4-Di-*O*-benzoyl-3,6-dideoxy-*L-arabino-*hexopyranose* (**5**). — A solution of compound **4** (240 mg, 0.67 mmol) in THF (0.5 mL) was added to a 1M solution of disiamylborane in THF (3 mL) at room temperature. The reaction solution was stirred for 20 h at room temperature. Water was then added, and the resulting mixture was stirred for 30 min. The quenched reaction mixture was cooled to 0° and slowly mixed with 30% hydrogen peroxide (0.3 mL). The pH of the solution was adjusted between pH 7 and 8 by adding 3N NaOH. After the THF was removed *in vacuo*, the solution was extracted several times with dichloromethane. The organic extracts

were combined and washed with water, dried over anhydrous magnesium sulfate, and concentrated to a syrup. The crude product was purified by flash chromatography (1:19 EtOAc–benzene) to give **5** (149 mg, 62%): ^{1}H-n.m.r. data ($CDCl_3$): δ 8.20–7.30 (10 H, m, Ar Hs), 5.27 (1 H, d, J 4.0 Hz, H-1), 5.25 (0.5 H, m, H-2), 5.20 (1 H, m, H-4), 4.33 (1 H, m, H-5), 2.82 (1 H, d, J 3.8 Hz, OH), 2.41 (1 H, bd, J 4.0 Hz, H-3), and 1.30 (3 H, d, J 6.0 Hz, 5-Me).

Anal. Calc. for $C_{20}H_{18}D_2O_6$: C, 67.01; H and ^{2}H, 6.19. Found: C, 67.18; H, 6.06.

(3S)-[2,3-$^2H_2$]-3,6-Dideoxy-L-arabino-*hexopyranose* (**6**). — Compound **5** (150 mg, 0.42 mmol) was dissolved in chloroform (2.5 mL), and 0.5M sodium methoxide in methanol (2.5 mL) was added. The reaction mixture was stirred for 30 min at 0° and then diluted with water (10 mL). The organic layer was separated and extracted several times with water. The aqueous extracts were combined, treated with Dowex-50 [H^+], and concentrated. In order to facilitate the n.m.r. peak differentiation and fully characterize the structure assigned, the crude product was methylated with 5% HCl in methanol. The resulting crude methyl ascaryloside (55 mg) was dissolved in pyridine (1.25 mL) and mixed with *p*-bromobenzoyl chloride (160 mg, 0.73 mmol) at 4°. The reaction mixture was stirred for 24 h at room temperature, followed by methanol quenching and concentration under reduced pressure. The *p*-bromobenzoylated ascaryloside was purified by flash chromatography (2:98 EtOAc–benzene) to give product **6** (182 mg, 82%): ^{1}H-n.m.r. data ($CDCl_3$) : δ 8.00–7.55 (8 H, m, ArHs), 5.12 (1 H, m, H-4), 4.71 (1 H, s, H-1), 4.00–4.12 (1 H, m, H-5), 3.47 (3 H, s, OMe), 2.38 (1 H, d, $J_{3,4}$ 5.0 Hz, H-3), and 1.30 (3 H, d, $J_{5,6}$ 6.0 Hz, 5-Me). ^{13}C-n.m.r. data ($CDCl_3$): δ 164.5 (2 × C=O), 131.6–128.2 (Ar CS), 97.2 (C-1), 70.5 (C-2)*, 70.4 (C-4)*, 66.3 (C-5), 54.8 (OMe), 29.4 (C-3), and 17.6 (C-6).

Anal. Calc. for $C_{21}H_{18}D_2Br_2O_6$: C, 47.73; H and ^{2}H, 4.20; Br, 29.89. Found: C, 47.82; H, 4.08; Br, 29.80.

Methyl 2,3-O-benzylidene-6-deoxy-α-L-*mannopyranoside* (**8**). — A mixture of methyl *α*-L-rhamnoside (**7**) (4.3 g, 26.2 mmol), benzaldehyde dimethyl acetal (4.0 g, 26.3 mmol), and *p*-toluenesulfonic acid (40 mg, 0.21 mmol) was refluxed in dry DMF (11 mL) at 60° under reduced pressure (15 torr). At the end of the third hour, additional benzaldehyde dimethyl acetal (2.0 g, 13.1 mmol) in dry DMF (1 mL) was added. After the reaction was refluxed for an additional 3 h, the DMF was evaporated *in vacuo*, and the solution was neutralized with sodium carbonate (10% aq. solution). The aqueous solution was extracted with dichloromethane, and the pooled organic extracts were dried over anhydrous magnesium sulfate and concentrated. Compound **8** was purified by medium-pressure liquid chromatography (1:9 EtOAc–benzene) to give two epimers (4.62 g, 72%): ^{1}H-n.m.r. data ($CDCl_3$) of these two diastereomers: δ 7.62–7.33 (10 H total, m, ArHs), 6.10, 5.85 (1 H each, s, acetalic-H), 4.96, 4.87 (1 H each, s, H-1), 4.35, 4.19 (1 H each, m, H-3), 4.18, 4.08 (1 H each, dd, J 7.8 Hz, 5.3, H-4), 3.65 (2 H, m, H-5s), 3.45 (1H, d, J 7.3 Hz, H-2), 3.40 (1 H, d, J 7.4 Hz, H-2), 3.37, 3.33 (3 H each, s, OMe), and 1.30 and 1.23 (3 H each, d, J 6.2 Hz, 5-Me).

Methyl-2-O-benzoyl-3-bromo-3,6-dideoxy-α-L-*altropyranoside* (**9**). — Barium carbonate (3.84 g, 19.5 mmol) and *N*-bromosuccinimide (2.56 g, 14.4 mmol) were added

to a solution of compound **8** (3.20 g, 12 mmol) in dry carbon tetrachloride (250 mL). The reaction was refluxed for 5 h. The precipitate was then removed, and the filtrate was concentrated. The crude product was purified by flash chromatography (1:1 CH_2Cl_2–benzene) to give **9** (3.1 g, 76%): m.p. 52–54° (lit. [10]m.p. 52–53°); ^{1}H-n.m.r. data ($CDCl_3$): δ 8.2–7.5 (5 H, m, ArHs), 5.53 (1 H, bd, J 3.0 Hz, H-2), 4.75 (1 H, s, H-1), 4.55 (1 H, dd, J 3.5 Hz, 3.0, H-3), 4.05 (1 H, m, H-5), 3.6 (1 H, dd, J 8.0 Hz, 3.5, H-4), 3.43 (3 H, s, OMe), and 1.40 (3 H, d, J 6.0 Hz, 5-Me). ^{13}C-n.m.r. data ($CDCl_3$): δ 164.5 (C = O), 133.4–128.3 (ArCs), 98.9 (C-1), 72.9 (C-2), 68.5 (C-4), 65.6 (C-5), 55.2 (OMe), 52.3 (C-3), and 18.9 (C-6).

*Methyl (3S)-[3-^{2}H]-3,6-dideoxy-α-*L*-arabino-hexopyranoside* (**11**). — To a solution of lithium aluminum deuteride (150 mg, 3.6 mmol) in dry THF (10 mL) was added a solution of compound **9** (363 mg, 1.1 mmol) in THF (28 mL). The reaction mixture was refluxed for 1 h, and the excess deuteride was quenched with saturated aq. sodium sulfate. The precipitate was removed, and the filtrate was concentrated. The crude product was *p*-bromobenzoylated and characterized by n.m.r. spectroscopy as described previously for compound **6**. High-resolution f.a.b-m.s.: calc. for $C_{21}H_{20}DBr_2O_6$ $(M + H)^+$, 527.9784; found, 527.9786.

*Methyl 3,4-O-benzylidene-6-deoxy-*D*-galactopyranoside* (**14**). — This compound was synthesized from 6-deoxy-D-galactopyranose which was derived from galactose[6]. The crude methyl 6-deoxy-D-galactopyranoside (50 mg, 0.28 mmol), prepared from acidic methanolysis (5% HCl/MeOH) of 6-deoxy-D-galactose, was dissolved in freshly distilled pyridine (2 mL) and mixed with α,α-dibromotoluene (99.6 mg, 0.4 mmol). The solution was heated under reflux for 2 h, followed by dilution with chloroform, extraction with a saturated copper(II) sulfate solution, and washing twice with water. The organic layer was collected, dried over anhydrous sodium sulfate, filtered, and concentrated. The product was purified by flash chromatography (2:95 MeOH–CH_2Cl_2) to give **14** (42 mg, 56%): ^{1}H-n.m.r. data ($CDCl_3$) of the β-isomer: δ 7.54–7.33 (5 H, m, ArHs), 6.17 (1 H, s, acetalic-H), 4.79 (1 H, d, J 4.0 Hz, H-1), 4.42 (1 H, m, H-5), 4.15–4.04 (2 H, m, H-3, H-4), 3.92 (1 H, dd, J 7.0 Hz, 4.0, H-2), 3.45 (3 H, s, OMe), and 1.37 (3 H, d, J 6.5 Hz, 5-Me). ^{13}C-n.m.r. data ($CDCl_3$) of the β-isomer: δ 139.1, 128.4, 126.8, 126.2 (ArCs), 102.9 (C-1), 98.9 (acetalic-C), 77.5 (C-4), 76.0 (C-3), 67.6 (C-5), 63.6 (C-2), 55.6 (OMe), and 16.4 (C-6). High-resolution f.a.b-m.s.: calc. for $C_{14}H_{19}O_5$ $(M + H)^+$, 267.1232; found, 267.1246.

*Methyl-4-O-benzoyl-3-bromo-3,6-dideoxy-β-*D*-gulopyranoside* (**15**). — In freshly distilled carbon tetrachloride (10 mL) were mixed compound **14** (80 mg, 0.3 mmol), barium carbonate (120 mg, 0.61 mmol), and *N*-bromosuccinimide (100 mg, 0.56 mmol). The reaction was heated under reflux for 6 h. The solution was diluted with chloroform, washed with water, dried over anhydrous sodium sulfate, filtered, and then concentrated. The product was purified by flash chromatography (3:22 EtOAc–benzene) to give **15** (80 mg, 77%): ^{1}H-n.m.r. data ($CDCl_3$) : δ 8.11 (2 H, dd, J 8.2 and 1.4 Hz, ArHs), 7.56 (1 H, m, ArH), 7.45 (2 H, m, ArHs), 5.31 (1 H, dd, J 3.0 and 1.2 Hz, H-4), 4.65 (1 H, d, J 7.7 Hz, H-1), 4.59 (1 H, dd, J 3.4 and 3.0 Hz, H-3), 4.54 (1 H, dq, J 6.5 and 1.2 Hz, H-5), 3.75 (1 H, ddd, J 7.7, 4.5 and 3.4 Hz, H-2), 3.60 (3 H, s, OMe), 2.53 (1 H, d, J 4.5 Hz, OH), and

1.28 (3 H, d, *J* 6.5 Hz, 5-Me). ^{13}C-n.m.r. data ($CDCl_3$) : δ 165.5 (C=O), 133.7, 130.0, 129.9, 129.0, 128.3 (ArCs), 102.1 (C-1), 74.0 (C-4), 67.6 (C-5)*, 67.4 (C-2)*, 57.2 (OMe), 52.6 (C-3), and 16.3 (C-6). High-resolution f.a.b-m.s.: calc. for $C_{14}H_{18}BrO_5$ $(M + H)^+$, 345.0338; found, 345.0306.

*Methyl 3,4-anhydro-6-deoxy-β-*D*-galactopyranoside* (**16**). — Compound **15** (41.8 mg, 0.12 mmol) was dried thoroughly and dissolved in a 1:1 mixture of dichloromethane and methanol (2.0 mL). The solution was cooled to 0° under nitrogen and mixed with one equivalent of freshly prepared NaOMe in methanol. The reaction was stirred overnight at 0°, followed by removal of the solvent *in vacuo*. The crude product was used directly in the next reaction. ^{1}H-n.m.r. data ($CDCl_3$) : δ 4.04 (1 H, d, *J* 7.3 Hz, H-1), 4.03 (1 H, q, *J* 6.5 Hz, H-5), 3.65 (1 H, d, *J* 7.3 Hz, H-2), 3.48 (3 H, s, OMe), 3.23 (1 H, d, *J* 3.6 Hz, H-3), 3.03 (1 H, d, *J* 3.6 Hz, H-4), and 1.38 (3 H, d, *J* 6.5 Hz, 5-Me). ^{13}C-n.m.r. data ($CDCl_3$) : δ 104.2 (C-1), 68.9 (C-2), 66.7 (C-5), 56.5 (OMe), 54.9 (C-3), 53.4 (C-4), and 17.3 (C-6). High-resolution c.i.-m.s.: calc. for $C_7H_{16}NO_4$ $(M + NH_4^+)$, 178.1079; found, 178.1080. Compound **16** was also converted to its acetate derivative to further confirm its structure. ^{1}H-n.m.r. data ($CDCl_3$) of the resulting methyl *2-O-acetyl-3,4-anhydro-6-deoxy-β-*D*-galactopyranoside*: δ 4.74 (1 H, d, *J* 7.4 Hz, H-2), 4.24 (1 H, d, *J* 7.4 Hz, H-1), 4.06 (1 H, q, *J* 6.5 Hz, H-5), 3.44 (3 H, s, OMe), 3.12 (1 H, d, *J* 3.5 Hz, H-3), 3.01 (1 H, d, *J* 3.5 Hz, H-4), 2.12 (3 H, s, $CH_3C=O$), and 1.40 (3 H, d, *J* 6.5 Hz, 5-Me).

*Methyl (3S)-[3-^{2}H]-3,6-dideoxy-β-*D*-xylo-hexopyranoside* (**19**). — To a chilled solution of compound **16** (10 mg, 63 μmol) in THF (2 mL) was added lithium aluminum deuteride (8 mg, 0.19 mmol). The reaction mixture was refluxed for 6 h. Excess reducing agent was quenched by a few drops of ethyl acetate. The white precipitate was removed by filtration, and the filtrate was then concentrated. ^{1}H-n.m.r. data ($CDCl_3$) of the crude product: δ 4.33 (1 H, d, *J* 8.1 Hz, H-1), 3.92 (1 H, m, H-4), 3.75 (1 H, m, H-5), 3.48 (1 H, m, H-2), 3.40 (3 H, s, OMe), 2.46 (1 H, m, H-3), and 1.14 (3 H, d, *J* 6.6 Hz, 5-Me). The crude product was dried and dissolved in pyridine (2 mL). *p*-Bromobenzoyl chloride (120 mg, 0.55 mmol) was added, and the reaction was heated overnight at 50–60°. The pyridine was removed by repeated co-evaporating with benzene *in vacuo*. The benzoylated product, methyl (3*S*)-[3-^{2}H]-2,4-di-*O*-(*p*-bromobenzoyl)-3,6-didexoy-β-D-*xylo*-hexopyranoside, was purified by flash chromatography (3:22 EtOAc–hexane) to give product **19** (4.2 mg, 41%): ^{1}H-n.m.r. data ($CDCl_3$) : δ 7.98 (2 H, d, *J* 8.9 Hz, ArHs), 7.85 (2 H, d, *J* 8.6 Hz, ArHs), 7.56 (4 H, dd, *J* 8.9 and 8.6 Hz, ArHs), 5.22 (1 H, d, $J_{3,4}$ 3.1 Hz, H-4), 5.20 (1 H, dd, $J_{1,2}$ 7.9, $J_{2,3}$ 5.0 Hz, H-2), 4.56 (1 H, d, $J_{1,2}$ 7.9 Hz, H-1), 3.96 (1 H, q, $J_{5,6}$ 6.5 Hz, H-5), 3.55 (3 H, s, OMe), 2.53 (1 H, dd, $J_{2,3}$ 5.0, $J_{3,4}$ 3.1 Hz, H-3), and 1.28 (3 H, d, $J_{5,6}$ 6.5 Hz, 5-Me). High-resolution f.a.b-m.s.: calc. for $C_{21}H_{20}DBr_2O_6$ $(M + H)^+$, 527.9784; found, 527.9786.

*1,2:5,6-Di-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl-α-*D*-glucofuranose* (**21**). — Triflic anhydride (5.04 g, 17.9 mmol) in dichloromethane (50 mL) was added to a chilled (−20°) mixture of pyridine (3 mL) and dichloromethane (320 mL). To this solution was added 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[16] (**20**) (3.0 g, 11.5 mmol) in dichloromethane (80 mL). The reaction mixture was stirred for 2 h at −20° before warming to room temperature. The solution was then extracted with 5% aq.

sodium bicarbonate, followed by water. The organic layer was dried with anhydrous sodium sulfate and concentrated. Residual pyridine was removed by repeatedly resuspending the crude product in benzene and concentrating *in vacuo*. The yield of the triflate **21** was quantitative, and it was used without further purification to synthesize the deoxyiodo sugar **22**.

*3-Deoxy-3-iodo-1,2:5,6-Di-*O*-isopropylidene-α-*D*-allofuranose* (**22**). — Triflate **21** (4.5 g, 11.5 mmol) was dissolved in benzene (150 mL), and tetrabutylammonium iodide (11.1 g, 30 mmol) was added. The reaction was then heated under reflux overnight (18 h). The cooled solution was sequentially washed with 150-mL portions of water, 5% aq. sodium bisulfite, saturated aq. sodium bicarbonate, and water. The organic extract was then dried over anhydrous sodium sulfate and concentrated. This crude material was purified by flash chromatography (1:99 acetone–benzene) to give the desired product **22** (6.6 g, 67%): ^{1}H-n.m.r. data ($CDCl_3$) : δ 5.75 (1 H, d, J 4.0 Hz, H-1), 4.54 (1 H, dd, J 4.0 and 4.0 Hz, H-2), 4.26 (1 H, m, H-5), 4.19 (1 H, dd, J 10.0 and 3.8 Hz, H-4), 4.02 (2 H, m, H-6), 3.70 (1 H, dd, J 10.0 and 4.0 Hz, H-3), 1.49 (3 H, s, Me), 1.42 (3 H, s, Me), and 1.31 (6 H, s, 2 × Me). ^{13}C-n.m.r. data ($CDCl_3$) : δ 103.1 (C-1), 82.9 (C-4), 81.7 (C-2), 75.4 (C-5), 65.8 (C-6), 26.7 (Me), 26.6 (Me), 26.5 (Me), 25.2 (Me), and 19.3 (C-3).

*(3S)-[3-^{2}H]-3-Deoxy-1,2:5,6-di-*O*-isopropylidene-α-*D*-ribo-hexofuranose* (**23**). — The deoxyiodo sugar **22** (1.4 g, 3.8 mmol) was dissolved in absolute ethanol (50 mL) and cooled to 0°. Sodium borodeuteride (375 mg, 8.9 mmol) was then added to the stirred solution, followed by cautious addition of hydrated nickel chloride (75 mg, 0.31 mmol). The mixture was then allowed to warm to room temperature, and the reaction was allowed to proceed for 2.5 h. After the reaction was completed, the ethanol was removed *in vacuo*, and the resultant black residue was resuspended in chloroform (200 mL). This solution was then washed with saturated aq. sodium bicarbonate (200 mL) and water (200 mL). The organic layer was dried over anhydrous sodium sulfate and filtered through fluted filter paper to remove the remaining nickel boride reagent. The solvent was then removed *in vacuo*, and the residue was purified by flash chromatography (1:99 acetone–benzene) to give the desired product **23** (560 mg, 60%): ^{1}H-n.m.r. data ($CDCl_3$) : δ 5.79 (1 H, d, $J_{1,2}$ 3.6 Hz, H-1), 4.74 (1 H, d, $J_{1,2}$ 3.6 Hz, H-2), 4.10 (3 H, m, H-4, H-5 and H-6), 3.82 (1 H, m, H-6), 2.15 (1 H, d, $J_{3,4}$ 3.6 Hz, H-3), 1.50 (3 H, s, Me), 1.42 (3 H, s, Me), 1.34 (3 H, s, Me), and 1.30 (3 H, s, Me). ^{13}C-n.m.r. data ($CDCl_3$) : δ 105.6 (C-1), 80.4 (C-2), 78.6 (C-4), 76.8 (C-5), 67.2 (C-6), 35.2 (C-3), 26.7 (Me), 26.6 (Me), 26.5 (Me), and 25.2 (Me). High-resolution f.a.b-m.s.: calc. for $C_{12}H_{20}DO_5$ $(M + H)^+$, 246.1467; found, 246.1445.

*Methyl 4,6-*O*-benzylidene-3-deoxy-3-iodo-α-*D*-glucopyranoside* (**26**). — The Grignard reagent, methyl magnesium iodide, was prepared by adding methyl iodide (1.5 g, 10.6 mmol) to magnesium turnings (0.27 g, 11.1 mmol) in tetrahydrofuran (50 mL) and heating under reflux under nitrogen for 2 h. Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside[20] (**25**) (2.1 g, 7.8 mmol), dissolved in tetrahydrofuran (50 mL), was then added, and the reaction was heated at reflux for 2 h. After the reaction was complete, the mixture was allowed to cool to room temperature and was treated with crushed ice. 1 M Hydrochloric acid was added dropwise to bring the mixture to

neutral pH. The solution was concentrated to a minimal volume, redissolved in chloroform, and washed with saturated aq. sodium bicarbonate and water. The organic fraction was dried over anhydrous sodium sulfate and concentrated. The crude product was recrystallized from hot ethanol, giving the desired compound **26** (2.4 g, 78%) as white crystals: m.p. 193–195° (lit.[21] m.p. 195–196°); ^{1}H-n.m.r. data ($CDCl_3$) : δ 7.56–7.36 (5 H, m, Ar Hs), 5.56 (1 H, s, acetalic-H), 4.72 (1 H, d, J 3.6 Hz, H-1), 4.25 (1 H, dd, J 9.1 and 3.5 Hz, H-6), 4.17 (1 H, dd, J 10.5 and 10.5 Hz, H-3), 3.93–3.57 (4 H, m, H-2, H-4, H-5 and H-6), 3.41 (3 H, s, OCH_3), and 2.50 (1 H, d, J 9.6 Hz, OH). ^{13}C-n.m.r. data ($CDCl_3$) : δ 129–126 (ArCs), 101.7 (acetalic-C), 99.5 (C-1), 81.5 (C-4), 74.2 (C-2), 68.5 (C-6), 65.3 (C-5), 55.5 (OMe), and 33.1 (C-3).

Anal. Calc. for $C_{14}H_{17}IO_5$: C, 42.88; H, 4.37; I, 32.36. Found: C, 42.98; H, 4.48; I, 32.39.

*Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-deoxy-3-iodo-α-*D*-glucopyranoside* (**27**). — The deoxyiodo sugar **26** (1.2 g, 3.1 mmol) was dissolved in dichloromethane (120 mL). Benzoic anhydride (1.3 g, 5.8 mmol), triethylamine (0.51 g, 5.1 mmol), and 4-dimethylaminopyridine (0.4 g, 3.3 mmol) were added, and the mixture was heated at reflux for 2 h. The mixture was then allowed to cool to room temperature and was washed with saturated aq. sodium bicarbonate and water. The organic layer was then collected, and the solvent was evaporated to give an amber-colored syrup, which was purified by flash chromatography (1:99 acetone–benzene) to give 1.5 g of the desired compound **27** in quantitative yield: ^{1}H-n.m.r. data ($CDCl_3$) : δ 8.18–7.37 (10 H, m, ArHs), 5.62 (1 H, s, acetalic-H), 5.26 (1 H, dd, J 11.2 and 3.5 Hz, H-2), 4.99 (1 H, d, J 3.5 Hz, H-1), 4.54 (1 H, dd, J 11.2 and 11.2 Hz, H-3), 4.29 (1 H, dd, J 10.2 and 5.0 Hz, H-6), 3.95 (1 H, m, H-5), 3.77 (1 H, dd, J 11.2 and 11.2 Hz, H-4), 3.74 (1 H, dd, J 10.2 and 10.2 Hz, H-6), and 3.39 (3 H, s, OCH_3). ^{13}C-n.m.r. data ($CDCl_3$) : δ 133.1–125.7 (ArCs), 101.5 (acetalic-C), 97.5 (C-1), 81.6 (C-4), 74.5 (C-2), 68.2 (C-6), 65.0 (C-5), 55.0 (OMe), and 25.6 (C-3). High-resolution f.a.b-m.s.: calc. for $C_{21}H_{22}IO_6$ $(M + H)^+$, 497.0463; found, 497.0460.

*Methyl (3S)-[3-^{2}H]-2-*O*-benzoyl-4,6-*O*-benzylidene-3-deoxy-α-*D*-ribo-hexopyranoside* (**28**). — The protected deoxyiodo sugar **27** (400 mg, 0.81 mmol) was dissolved in absolute ethanol (30 mL) and cooled to 0° in an ice bath. Sodium borodeuteride (90 mg, 2.1 mmol) was then added, followed by the cautious addition of hydrated nickel chloride (90 mg, 0.38 mmol), causing the reaction mixture to assume the characteristic black color of the nickel boride reagent. The reaction was then run overnight (16 h) at room temperature. To recover the product, the solvent was removed *in vacuo*, and the black residue was purified by flash chromatography (1:99 acetone–benzene) to give the desired compound **28** (280 mg, 94%): ^{1}H-n.m.r. data ($CDCl_3$) : δ 8.13–7.37 (10 H, m, ArHs), 5.58 (1 H, s, acetalic-H), 5.15 (1 H, dd, J 12.0 and 3.5 Hz, H-2), 4.98 (1 H, d, J 3.5 Hz, H-1), 4.32 (1 H, dd, J 9.9 and 4.3 Hz, H-6), 3.86 (1 H, m, H-5), 3.78 (1 H, dd, J 9.9 and 9.9 Hz, H-6), 3.71 (1 H, dd, J 12.0 and 9.2 Hz, H-4), 3.46 (3 H, s, OMe), and 2.28 (1 H, dd, J 12.0 and 12.0 Hz, H-3). ^{13}C-n.m.r. data ($CDCl_3$) : δ 165.2 (C = O), 136.7–125.7 (ArCs), 101.3 (acetalic-C), 96.4 (C-1), 75.8 (C-4), 68.6 (C-2), 68.5 (C-6), 63.4 (C-5), 54.7 (OMe), and 28.7 (C-3).

Anal. Calc. for $C_{21}H_{21}DO_6$: C, 67.91; H and ^2H, 6.16. Found: C, 67.78; H, 6.15.

*Methyl (3S)-[3-^{2}H]-2,4-di-*O*-benzoyl-6-bromo-3,6-dideoxy-α-*D*-ribo-hexopyranoside* (**29**). — The deuterium-labeled sugar **28** (0.3 g, 0.81 mmol) was dissolved in carbon tetrachloride (15 mL). Barium carbonate (90 mg, 0.46 mmol), *N*-bromosuccinimide (200 mg, 1.1 mmol), and a trace amount of benzoyl peroxide (5 mg, 20 μmol) were then added to the stirred solution, and the mixture was heated at reflux for 2.5 h. The suspension was then filtered through Celite while hot, which was then washed with an additional amount of hot carbon tetrachloride (15 mL). The combined filtrates were concentrated, giving a pale-orange syrup, which was purified by flash chromatography (2:98 acetone–benzene) to give the desired compound **29** (207 mg, 57%): ^{1}H-n.m.r. data ($CDCl_3$): δ 8.09–7.41 (10 H, m, ArHs), 5.19 (1 H, dd, *J* 12.0 and 3.5 Hz, H-2), 5.16–5.11 (1 H, m, H-4), 5.09 (1 H, d, *J* 3.5 Hz, H-1), 4.18 (1 H, td, *J* 7.5 and 2.2 Hz, H-5), 3.66–3.47 (2 H, m, H-6), 3.61 (3 H, s, OMe), and 2.30 (1 H, dd, *J* 12.0 and 12.0 Hz, H-3). ^{13}C-n.m.r. data ($CDCl_3$): δ 165.0, 164.5 (C=O), 133.2–127.7 (ArCs), 95.7 (C-1), 69.0 (C-5), 68.6 (C-4), 68.0 (C-2), 54.7 (OMe), 31.4 (C-6), and 28.8 (C-3). High-resolution f.a.b-m.s.: calc. for $C_{21}H_{21}DBrO_6$ $(M + H)^+$, 450.0663; found, 450.0654.

*Methyl (3S)-[3-^{2}H]-2,4-di-*O*-benzoyl-3,6-dideoxy-α-*D*-ribo-hexopyranoside* (**30**). — Tributyltin hydride (120 mg, 0.41 mmol) and α,α′-azobisisobutyronitrile (AIBN) (a trace amount) were added to a solution of **29** (90 mg, 0.2 mmol) in anhydrous toluene (3 mL) under nitrogen. The reaction mixture was then heated to 80° and run overnight (16 h) with stirring. To recover the product **30**, the toluene was removed *in vacuo*, and the residue was purified by flash chromatography (1:9 EtOAc–hexane) to give the perbenzoylated dideoxy sugar **30** (59 mg, 80%): ^{1}H-n.m.r. data ($CDCl_3$): δ 8.05–7.34 (10 H, m, ArHs), 5.15 (1 H, dd, $J_{2,3}$ 12.1, $J_{1,2}$ 3.4 Hz, H-2), 4.96 (1 H, d, $J_{1,2}$ 3.4 Hz, H-1), 4.90 (1 H, dd, $J_{3,4}$ 12.1, $J_{4,5}$ 10.1 Hz, H-4), 4.09 (1 H, m, H-5), 3.61 (3 H, s, OMe), 2.21 (1 H, dd, $J_{2,3}$ 12.1, $J_{3,4}$ 12.1 Hz, H-3), and 1.26 (3 H, d, $J_{5,6}$ 6.8 Hz, 5-Me). ^{13}C-n.m.r. data ($CDCl_3$): δ 165.2, 164.9 (C=O), 133.6–127.8 (ArCs), 95.8 (C-1), 71.5 (C-5), 68.5 (C-4), 65.4 (C-2), 54.7 (OMe), 29.0 (C-3), and 16.9 (C-6). High-resolution f.a.b-m.s.: calc. for $C_{21}H_{22}DO_6$ $(M + H)^+$, 372.1557; found, 372.1533.

*Methyl (3S)-[3-^{2}H]-4-*O*-benzoyl-3,6-dideoxy-β-*D*-xylo-hexopyranoside* (**31**). — Compound **15** (20 mg, 50 μmol) was dissolved in absolute ethanol (2 mL). To this solution was slowly added sodium borodeuteride (10 mg, 0.26 mmol) and hydrated nickel chloride (25 mg, 0.11 mmol). The solution turned black and was allowed to stir for 12 h at room temperature. The black precipitate was removed by filtering through Celite, and the filtrate was diluted with dichloromethane. This solution was washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated. The product was purified by flash chromatography (3:19 EtOAc–benzene) to give **31** (9 mg, 66%): ^{1}H-n.m.r. data ($CDCl_3$): δ 8.10 (2 H, d, *J* 7.5 Hz, ArHs), 7.56 (1 H, m, ArH), 7.45 (2 H, m, ArHs), 5.19 (1 H, bs, H-4), 4.21 (1 H, d, *J* 7.7 Hz, H-1), 3.87 (1 H, q, *J* 6.5 Hz, H-5), 3.85 (1 H, m, H-2), 3.60 (3 H, s, OMe), 2.38 (1 H, m, H-3), and 1.26 (3 H, d, *J* 6.5 Hz, 5-Me). ^{13}C-n.m.r. data ($CDCl_3$): δ 166.0 (C=O), 133.3, 129.9, 129.7, 128.5 (ArCs), 106.3 (C-1), 72.9 (C-4), 71.0 (C-5), 66.4 (C-2), 57.1 (OMe), 34.8 (C-3), and 16.6 (C-6). High-resolution f.a.b-m.s.: calc. for $C_{14}H_{18}DO_5$ $(M + H)^+$, 268.1311; found, 268.1312.

When sodium borohydride was used as the reducing agent, the product **31** isolated gave an additional resonance at δ 1.79 (1 H, dd, J 14.0 and 11.6 Hz, H-3). For further confirmation, compound **31** (20.8 mg, 78 μmol) and *p*-bromobenzoyl chloride (26 mg, 0.12 mmol) were dissolved in freshly distilled pyridine (1 mL) and heated for 12 h at 50–60°. A few drops of methanol were added to quench the reaction, and the pyridine was removed by coevaporating the residual solvent with benzene *in vacuo*. The product was purified by flash chromatography (1:49 EtOAc–benzene) to give the perbenzoylated product (12 mg, 46%, structure not shown): ^{1}H-n.m.r. data ($CDCl_3$) : δ 8.11 (2 H, d, J 7.6 Hz, ArHs), 7.87 (2 H, d, J 8.5 Hz, ArHs), 7.56 (2 H, d, J 8.5 Hz, ArHs), 7.60–7.55 (1 H, m, ArH), 7.46 (2 H, dd, J 7.6 and 6.8 Hz, ArHs), 5.28–5.20 (2 H, m, H-2 and H-4), 4.58 (1 H, d, J 7.5 Hz, H-1), 3.95 (1 H, bq, J 6.2 Hz, H-5), 3.56 (3 H, s, OMe), 2.58 (1 H, dd, J 5.1 and 3.2 Hz, H-3), and 1.28 (3 H, d, J 6.2 Hz, 5-Me).

*Methyl 3,6-dibromo-3,6-dideoxy-α-*D*-allopyranoside* (**33**). — A mixture of methyl α-D-glucopyranoside (1.0 g, 5.1 mmol, dried and finely ground), 2,4,5-tribromoimidazole (3.2 g, 11 mmol), and triphenylphosphine (5.4 g, 20.6 mmol) in toluene (100 mL) was stirred for 1 h at 75° and then for 4 h at a bath temperature of 110°. After cooling to room temperature, the product was stirred for 5 min with aq. sodium bicarbonate (100 mL). Crystalline iodine was added portionwise until the organic layer remained iodine colored, and the mixture was then stirred for another 10 min. Aq. sodium thiosulfate was added to quench the excess iodine. The organic layer was collected, and the aqueous layer was extracted four times with dichloromethane. The combined organic extracts were dried with anhydrous sodium sulfate and concentrated, yielding a dark brown syrup. This syrup contained a large amount of triphenylphosphine oxide, much of which was removed by its ipitation with diethyl ether. After concentration, the remaining material was further purified by flash chromatography (1:49 acetone–benzene) yielding the desired product **33** (1.2 g, 72%). To facilitate structural characterization, compound **33** was perbenzoylated, and the n.m.r. and m.s. data were shown to be that of the perbenzoylated derivative of **33**: ^{1}H-n.m.r. data ($CDCl_3$) : δ 8.15–7.30 (10 H, m, ArHs), 5.39 (1 H, dd, J 4.1 and 4.1 Hz, H-4), 5.14 (3 H, m, H-1, H-2 and H-3), 4.60 (1 H, m, H-5), 3.65 (2 H, m, H-6), and 3.32 (3 H, s, OMe). ^{13}C-n.m.r. data ($CDCl_3$) : δ 165.4, 164.9 (C=O), 134.7–128.6 (ArCs), 97.1 (C-1), 68.7 (C-2), 68.0 (C-4), 66.0 (C-5), 56.3 (OMe), 49.4 (C-3), and 32.2 (C-6). High-resolution f.a.b-m.s.: calc. for $C_{21}H_{21}Br_2O_6$ $(M + H)^+$, 526.9706; found, 526.9687.

*Methyl (3S)-[3,6-$^2H_2$]-3,6-dideoxy-α-*D*-ribo-hexopyranoside* (**34**). — A solution of the dibrominated compound **33** (1.2 g, 3.75 mmol) in tetrahydrofuran (15 mL) was added dropwise to a cooled suspension of lithium aluminum deuteride (0.8 g, 20.5 mmol) in THF (10 mL). After refluxing for 16 h under nitrogen, the solution was cooled and quenched by cautious addition of saturated aq. ammonium chloride. The resulting grey residue was filtered through Celite, and the trapped precipitate was washed with methanol. The filtrates were combined, dried over anhydrous sodium sulfate, and concentrated, yielding a crude product which was purified by flash chromatography (1:19 methanol–chloroform) to give pure **34** (135 mg, 22%): ^{1}H-n.m.r. data ($CDCl_3$) : δ 4.53 (1 H, d, $J_{1,2}$ 3.4 Hz, H-1), 3.68 (1 H, dd, $J_{2,3}$ 11.5, $J_{1,2}$ 3.4 Hz, H-2), 3.45 (1 H, m, H-5),

3.33 (3 H, s, OMe), 3.25 (1 H, dd, $J_{3,4}$ 11.5, $J_{4,5}$ 5.9 Hz, H-4), 1.67 (1 H, dd, $J_{2,3}$ 11.5, $J_{3,4}$ 11.5 Hz, H-3), and 1.17 (2 H, d, $J_{5,6}$ 5.9 Hz, H-6). ^{13}C-n.m.r. data ($CDCl_3$) : δ 98.6 (C-1), 70.4 (C-2), 68.7 (C-5), 67.5 (C-4), 54.9 (OMe), 36.7 (C-3), and 17.2 (C-6).

Anal. Calc. for $C_7H_{12}D_2O_4$: C, 51.20; H and ^{2}H, 9.82. Found: C, 51.29; H, 9.76.

*Methyl (3*R*)-[3-^{2}H]-4,6-*O*-benzylidene-3-deoxy-α-*D*-ribo-hexopyranoside* (**36**). — A solution of methyl 4,6-*O*-benzylidene-2,3-di-*O*-(*p*-tolylsulfonyl)-α-D-glucopyranoside[20] (**35**) (4.0 g, 6.7 mmol) in tetrahydrofuran (20 mL) was added dropwise to a cooled suspension of lithium aluminum deuteride (0.75 g, 17.9 mmol) in THF (5 mL). After refluxing for 18 h under argon, the solution was cooled and quenched by cautious addition of saturated aq. ammonium chloride. The resulting white residue was filtered through Celite, and the trapped precipitate was washed with ether. The filtrates were combined, washed with water, and dried over anhydrous sodium sulfate. The solvent was then removed *in vacuo*, yielding a crude product which was partially purified by flash chromatography (1:19 acetone–benzene). Further purification by recrystallization from ether with petroleum ether gave the deuterated deoxy sugar **36** (1.2 g, 65%): m.p. 164–165° (lit.[27] m.p. 164–165°); ^{1}H-n.m.r. data ($CDCl_3$) : δ 7.48–7.33 (5 H, m, ArHs), 5.52 (1 H, s, acetalic-H), 4.67 (1 H, d, *J* 3.7 Hz, H-1), 4.26 (1 H, dd, *J* 15.8 and 10.2 Hz, H-6), 3.78 (1 H, ddd, *J* 11.3, 4.5 and 3.7 Hz, H-2), 3.72–3.68 (2 H, m, H-5, H-6), 3.53 (1 H, dd, *J* 9.8 and 4.5 Hz, H-4), 3.47 (3 H, s, OMe), 2.27 (1 H, dd, *J* 4.5 and 4.5 Hz, H-3), and 2.05 (1 H, d, *J* 11.3 Hz, 2-OH). ^{13}C-n.m.r. data ($CDCl_3$) : δ 133.5–128.6 (ArCs), 101.7 (acetalic-C), 99.1 (C-1), 76.4 (C-4), 69.4 (C-6), 67.6 (C-2), 64.0 (C-5), 55.3 (OMe), and 33.8 (C-3).

*Methyl (3*R*)-[3-^{2}H]-4-O-benzoyl-6-bromo-3,6-dideoxy-α-*D*-ribo-hexopyranoside* (**37**). — Compound **36** (620 mg, 2.3 mmol) was dissolved in carbon tetrachloride (33 mL). Barium carbonate (250 mg, 1.3 mmol), *N*-bromosuccinimide (460 mg, 2.6 mmol), and a trace amount of benzoyl peroxide (5 mg, 20 μmol) were then added to the stirred solution, and the mixture was heated under reflux for 2.5 h. The resulting suspension was filtered through Celite while hot, washing with additional hot carbon tetrachloride (15 mL). The combined filtrates were concentrated, giving a pale-orange syrup, which was purified by flash chromatography (1:19 acetone–benzene) to give the desired compound **37** (500 mg, 62%): ^{1}H-n.m.r. data ($CDCl_3$) : δ 8.08–7.41 (10 H, m, ArHs), 5.19 (1 H, dd, *J* 4.8 and 3.3 Hz, H-2), 5.16 (1 H, m, H-4), 5.08 (1 H, d, *J* 3.3 Hz, H-1), 4.17 (1 H, ddd, *J* 9.7, 7.3 and 2.3 Hz, H-5), 3.56–3.25 (2 H, m, H-6), 3.56 (3 H, s, OCH_3), and 2.39 (1 H, dd, *J* 4.8 and 4.8 Hz, H-3). ^{13}C-n.m.r. data ($CDCl_3$) : δ 165.2 (C=O), 133.5–128.6 (ArCs), 98.6 (C-1), 69.6 (C-4)*, 69.4 (C-2)*, 66.7 (C-5), 55.5 (OMe), 33.4 (C-3), and 32.2 (C-6).

*Methyl (3*R*)-[3-^{2}H]-2,4-di-O-benzoyl-6-bromo-3,6-dideoxy-α-*D*-ribo-hexopyranoside* (**38**). — The deuterated sugar **37** (100 mg, 0.29 mmol) was dissolved in dichloromethane (7 mL). Benzoic anhydride (100 mg, 0.44 mmol), triethylamine (58 mg, 0.57 mmol), and 4-dimethylaminopyridine (50 mg, 0.41 mmol) were added, and the reaction was heated for 2 h at reflux. The mixture was then allowed to cool to room temperature and was washed with 5% aq. sodium bicarbonate (15 mL) and water (15

mL). The organic layer was concentrated to give an amber-colored syrup. This was purified by flash chromatography (1:99 acetone–benzene), giving the desired compound **38** (130 mg, 100%): ^{1}H-n.m.r. data ($CDCl_3$) : δ 8.08–7.41 (10 H, m, ArHs), 5.16 (2 H, m, H-2, H-4), 5.08 (1 H, d, J 3.3 Hz, H-1), 4.17 (1 H, ddd, J 9.7, 7.3 and 2.3 Hz, H-5), 3.56 (2 H, m, H-6), 3.55 (3 H, s, OMe), and 2.55 (1 H, dd, J 4.8 and 4.8 Hz, H-3), ^{13}C-n.m.r. data ($CDCl_3$) : δ 165.0, 164.5 (C=O), 133.2–127.7 (ArCs), 95.7 (C-1), 69.0 (C-5)*, 68.6 (C-4)*, 68.0 (C-2)*, 54.7 (OMe), 31.4 (C-6), and 28.8 (C-3). High-resolution f.a.b-m.s.: calc. for $C_{21}H_{21}DBrO_6$ $(M + H)^+$, 450.0678; found, 450.0682.

*Methyl (3*R*)-[3-^{2}H]-2,4-di-*O*-benzoyl-3,6-dideoxy-α-*D*-ribo-hexopyranoside* (**39**). — Tributyltin hydride (108 mg, 0.37 mmol) and *a,a'*-azobisisobutyronitrile (AIBN) (a trace amount) were added to a solution of **38** (80 mg, 0.18 mmol) in anhydrous toluene (3 mL) under nitrogen. The reaction mixture was then heated to 80° and allowed to run overnight (16 h) with magnetic stirring. To recover the product **39**, the toluene was removed *in vacuo*, and the residue was purified by flash chromatography (1:19 EtOAc–hexane) to give the perbenzoylated dideoxy sugar **39** (53 mg, 79%): ^{1}H-n.m.r. data ($CDCl_3$) : δ 8.06–7.40 (10 H, m, ArHs), 5.15 (1 H, dd, $J_{2,3}$ 4.7, $J_{1,2}$ 3.4 Hz, H-2), 4.96 (1 H, d, $J_{1,2}$ 3.4 Hz, H-1), 4.89 (1 H, dd, $J_{4,5}$ 9.7, $J_{3,4}$ 4.7 Hz, H-4), 4.01 (1 H, m, H-5), 3.46 (3 H, s, OMe), 2.45 (1 H, dd, $J_{2,3}$ 4.7, $J_{3,4}$ 4.7 Hz, H-3), and 1.27 (3 H, d, $J_{5,6}$ 6.8 Hz, 5-Me). ^{13}C-n.m.r. data ($CDCl_3$) : δ 165.7, 165.4 (C=O), 133.2–128.4 (ArCs), 96.4 (C-1), 72.1 (C-5), 69.1 (C-4), 65.8 (C-2), 55.2 (OMe), 29.5 (C-3), and 17.5 (C-6). High-resolution f.a.b-m.s.: calc. for $C_{21}H_{22}DO_6$ $(M + H)^+$, 372.1573; found, 372.1571.

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