Syntheses and Characterizations of Chirally Deuteriated Glycerols

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(*1S*)- and (*1R*)-[1-^{2}H]-*sn*-Glycerols (**1a**) and (**1b**) have been stereoselectively synthesized from 1,6-anhydro-β-D-galactopyranose and characterized by ^{1}H and ^{13}C n.m.r. spectroscopy.

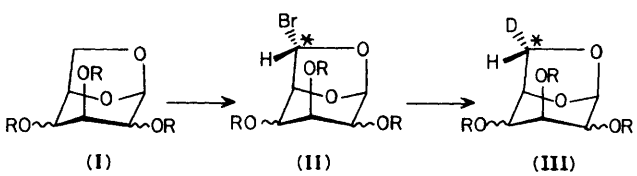
Glycerol has a plane of symmetry at C-2 and itself is achiral. In biosynthetic pathways, however, the prochiral C-1 and C-3 positions are recognized to give optically active glycerolipids.[1] For biosynthetic studies, *sn*-glycerols regio- and stereo-selectively deuteriated at C-1 or C-3 would provide a valuable means for determining stereochemistry of biochemical reactions at C-1 or C-3.[2,3] Recently,[3] an enzymatic diastereoselective preparation of (*3S*)- and (*3R*)-[3-^{2}H]-*sn*-glycerols was reported by Townsend and Mao, together with their use in studies on the biosynthesis of calvulanic acid. We now report the first chemical syntheses of the other two diastereoisomers chirally deuteriated at C-1 {(*1S*)-[1-^{2}H]-*sn*-glycerol (**1a**) and its (*1R*)-isomer (**1b**)} (Schemes 1 and 2) and characterization of their stereochemistry using ^{1}H and ^{13}C n.m.r. spectroscopy.

Previously,[4] we reported a general synthesis of (*6S*)-[6-^{2}H]-D-hexoses which involved two key reactions: photobromination of the 1,6-anhydro-β-D-hexopyranose derivative (**I**) to give the C-6 *exo*-bromide (**II**), followed by deuteride reduction to give the (*6S*)-deuteriated 1,6-anhydro derivative (**III**) (Scheme 1). The intermediate (**III**) has now been successfully used to prepare (*1S*)-[1-^{2}H]-*sn*-glycerol (**1a**). (*6S*)-Deuteriated 1,6-anhydro-β-D-galactopyranose (**2**)[4] was treated with $NaIO_4$ in water for 1 h and then with $NaBH_4$ to afford the alcohol (**3**) [95% isolated yield from (**2**)]. Acid hydrolysis of (**3**) with 60% trifluoroacetic acid gave the desired (**1a**) in 60% total yield. The use of the (*6S*)-deuteriated 1,6-anhydro-β-D-glucose[5] for the $NaIO_4$ oxidation was also successful; however, the reaction took a long time for completion, because of the all-*trans* orientation of the OH groups.

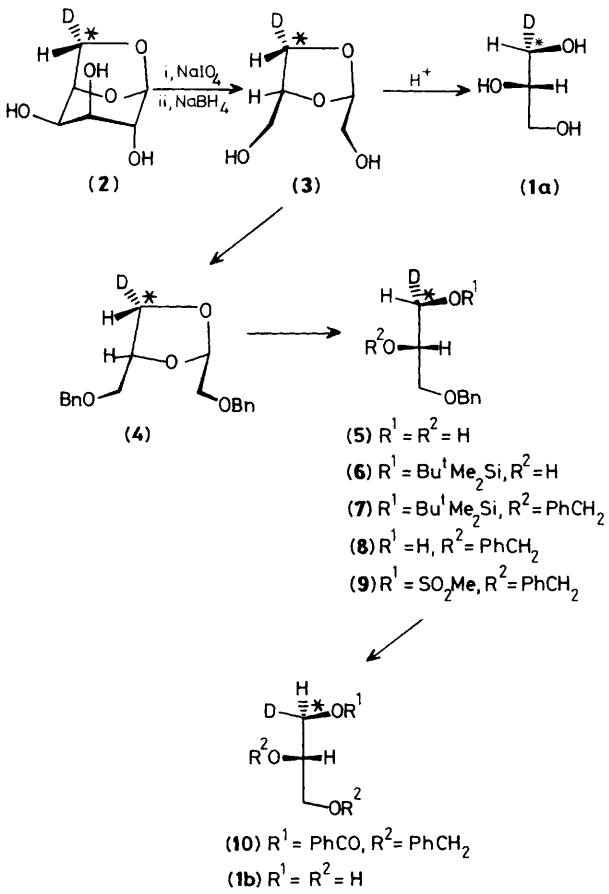
The (*1S*)-isomer was converted into (**1b**) *via* an S_N2 replacement of the 1-*O*-methylsulphonyl compound (**9**). The substrate (**9**) was obtained from (**3**) as follows: *O*-benzylation (benzyl bromide, sodium hydride in dimethylformamide), acid hydrolysis (60% aqueous trifluoroacetic acid), selective silylation at the primary hydroxy group (t-butyldimethylsilyl chloride, triethylamine, 4-*N*,*N*-dimethylaminopyridine in CH_2Cl_2), benzylation at C-2-OH, desilylation with tetra-n-butylammonium fluoride in oxolane, and methanesulphonylation (methanesulphonyl chloride in pyridine). The S_N2 reaction of (**9**) with sodium benzoate was carried out in dimethylformamide at 120 °C and completed in 6 h to give the (*1R*)-isomer (**10**), which was de-benzoylated with sodium methoxide in methanol and de-benzylated using H_2–Pd-black in methanol to give the desired (**1b**). The total yield from (**3**) was *ca.* 10—30%, the yield depending largely on the yield (50—70%) for the acid hydrolysis of (**4**), which required at least 6 h heating at 60—70 °C and careful separation of the desired (**5**) by silica gel column chromatography. The other reactions from (**3**) to (**1b**) proceeded almost quantitatively (90—100%).

400 MHz ^{1}H N.m.r. spectra of glycerol, (**1a**), and (**1b**) are compared in Figure 1 to characterize their stereochemistry. For (**1a**) one-proton signals at δ 3.65 (*pros*-1-H) disappeared, and new broad signals appeared at δ 3.56, while for (**1b**) one-proton signals at δ 3.56 (*proR*-1-H) disappeared, and new broad signals appeared at δ 3.64. These results are consistent with the diastereoselective deuteriation at C-1 of (**1a**) and (**1b**). They also allowed the first unequivocal assignments of the four prochiral protons (*proR*-1-H, *proS*-1-H, *proR*-3-H, and *proS*-3-H) of *sn*-glycerol by n.m.r. spectroscopy,[6—10] a hitherto unresolved problem in glycerolipid stereochemistry.[10]

In Figure 2, 100 MHz ^{13}C n.m.r. spectra of glycerol, (**1a**), and (**1b**) are compared; the intensity of the signal at δ 65.3 (C-1 and C-3) was considerably decreased, and new triplet signals appeared at δ 65.0 for both (**1a**) and (**1b**). These results



Scheme 1. R = Ac or PhCO.



Scheme 2

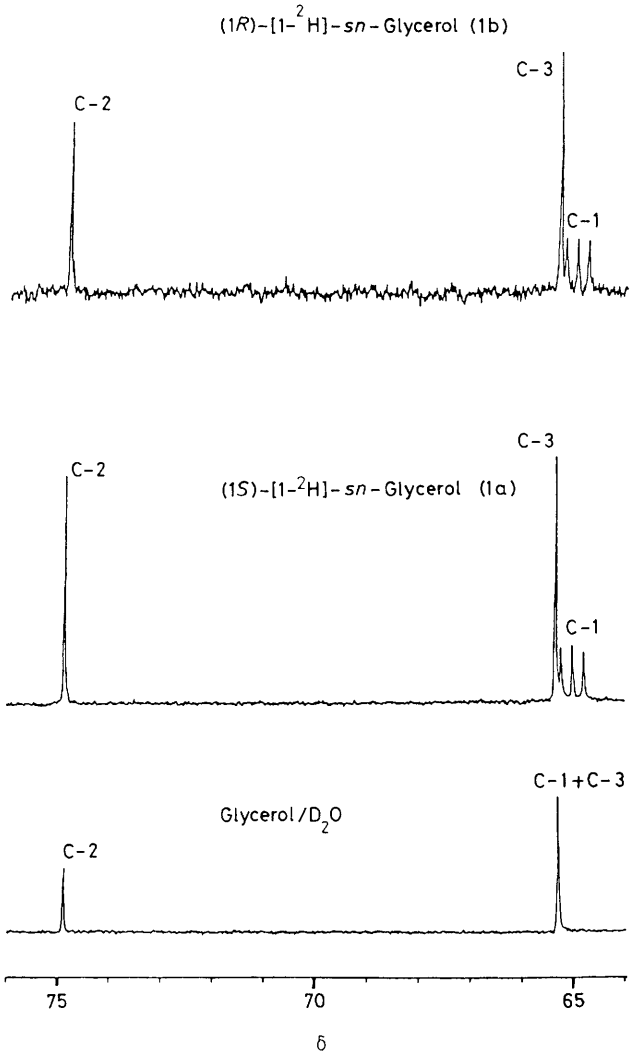


Figure 1. 400 MHz ^{1}H N.m.r. spectra of glycerol, (**1a**), and (**1b**) in D_2O. For (**1a**) and (**1b**), partially relaxed spectra (180°–*t*–90° pulse sequence) were used to separate the methine proton signals at C-1.

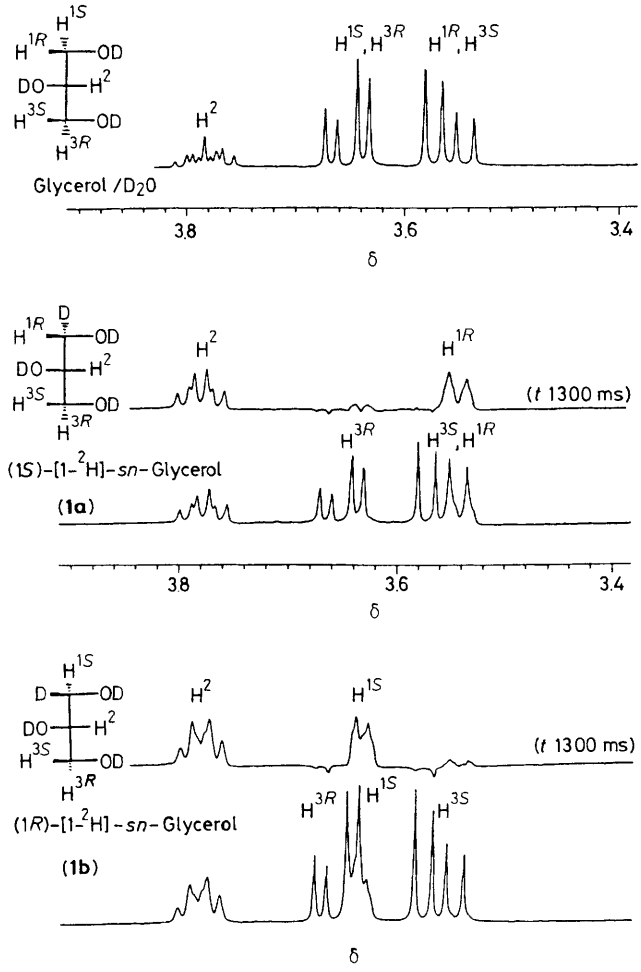


Figure 2. Complete ^{1}H-decoupled ^{13}C n.m.r. spectra of glycerol, (**1a**), and (**1b**) in D_2O.

also agree with selective mono-deuteriation at C-1. The chemical shifts of C-1 in (**1a**) and (**1b**) show a significant isotope shift (*ca.* 0.35 p.p.m.) compared with C-1 in glycerol. Isotope shifts were also detected at C-2 (0.07 p.p.m.) and C-3 (0.01—0.03 p.p.m.), although they were much smaller than the shift for C-1. Similar isotope shifts were observed for tripalmitins chirally deuteriated at C-1.[10] The isotope shift in ^{13}C n.m.r. has been reported to reflect the spatial distance from the deuterium atom or the linearity of the C–^{2}H axis.[11,12] We therefore had expected to obtain some information from the isotope shifts to differentiate between the two diastereoisomers (**1a**) and (**1b**). The shifts, however, did not show a sufficient substantial difference to be discriminating.

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