Synthesis and Characterization of Chirally Deuteriated *sn*-Glycerols

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(1*S*)-[1-²H]-*sn*-Glycerol (**1a**) was obtained in three steps from (6*S*)-[6-²H]-1,6-anhydro-β-D-galactopyranose and converted to the (1*R*)-isomer (**1b**) via an *S_N2* reaction of a 1-*O*-methane-sulfonylated derivative. The ¹H and ¹³C-NMR spectra well characterized their structure and stereochemistry.

Diastereoselectively deuteriated *sn*-glycerols (Schemes 1 and 2) are key compounds for biosynthetic studies of *O*-alkylated glycerolipids¹⁾ and other natural products,²⁾ as well as for conformational studies^{3~7)} on glycerolipids by NMR spectroscopy. Recently,²⁾ an enzymatic method has been presented to prepare diastereoisomeric *sn*-glycerols deuteriated at the C-3 position, which were applied to biosynthetic studies of clavulanic acid. In this paper, we present the first chemical syntheses of the other two stereoisomers **1a** and **1b** chirally deuteriated at the C-1 position, and characterize their structures with ¹H and ¹³C-NMR spectroscopy.⁸⁾

Results and Discussion

a) Syntheses of chirally deuteriated *sn*-glycerols (**1a** and **1b**)

In our previous studies,^{9~11)} a general synthetic method for (6*S*)-(6-²H)-D-hexoses was developed (Scheme 1). The method involved two key reactions: photobromination of the 1,6-anhydro-β-D-hexopyranose derivatives (**I**) to give the C-6 *exo* bromides (**II**), and a subsequent deuteride reduction to afford the (6*S*)-deuteriated compounds (**III**). In the present study, the intermediate 1,6-anhydro-sugar (**III**) was successfully used to prepare *sn*-glycerols chirally deuteriated at C-1 (**1a** and

Scheme 1.

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Scheme 2.

Fig. 1. 400 MHz ¹H-NMR Spectra of Glycerol, **1a** and **1b** in D₂O.

For **1a** and **1b**, partially relaxed spectra using the inversion recovery method with a 180-*t*-90 pulse sequence are also shown.

1b).

(6*S*)-Deuteriated 1,6-anhydro-β-D-galactopyranose (**2**), which had already been synthe-

sized in our preceding studies,^{10,11)} could be converted into **1a** with facility by oxidative cleavage with NaIO₄ (room temperature, 30

min), and subsequent NaBH_4 reduction and acid hydrolysis with 60% CF_3COOH . The total yield from **2** was *ca.* 60%. The use of a D-glucose isomer⁹ instead of **2** was also successful, but took a longer time to complete the NaIO_4 oxidation (room temperature, *ca.* 3 hr).

The conversion of the (2*S*)-isomer (**1a**) into the (1*R*)-isomer (**1b**) was accomplished *via* an $\text{S}_{\text{N}}2$ reaction of 1-*O*-methanesulfonylated compound **9** with sodium benzoate (Scheme 2). Substrate **9** was prepared from **3** by the following sequence of reactions: benzylation (benzyl bromide and sodium hydride in dimethylformamide), acid hydrolysis (60% aqueous trifluoroacetic acid at 60 °C, selective silylation at a primary hydroxyl group (^tbutyldimethylsilyl chloride, triethylamine and 4-*N,N*-dimethylamino pyridine in CH_2Cl_2), benzylation at OH-2, desilylation (tetra-*n*-butylammonium fluoride), and methanesulfonylation (methanesulfonyl chloride in pyridine). The $\text{S}_{\text{N}}2$ reaction of **9** with sodium

benzoate (in dimethylformamide at 120 °C for 6 hr) gave **10** in a *ca.* 90% yield, which was debenzoylated in sodium methoxide in methanol and debenzylated by hydrogenolysis with palladium black in methanol to give the desired **1b**.

b) ^1H and ^{13}C -NMR characterization of **1a** and **1b**.

Although diastereoselectively deuteriated *sn*-glycerols have already been prepared enzymatically,²⁾ the spectrometric behavior to characterize each of the diastereoisomers have not yet been reported. Moreover, the absolute stereochemistry induced by the enzymatic reactions seemed to be difficult to determine. In our diastereoselective syntheses, as has just been shown, the absolute stereochemistry in **1a** and **1b** was already established at C-5 and C-6 in starting compound **2**. Here, ^1H -NMR spectra of **1a** and **1b** in D_2O were successfully used to characterize their stereochemical structures

Fig. 2. 400 MHz ^1H -NMR Spectra of Tripalmitin and Its (1*S*)- and (1*R*)-Deuteriated Analogues in CDCl_3 .

(Fig. 1). The ^1H -NMR spectrum of **1a** showed that one proton signal at δ 3.65 ppm had disappeared, and one double doublet peak at δ 3.56 ppm had changed to a broad doublet at δ 3.54 ppm. These results confirmed that the H1*proS* of **1a** was selectively replaced with a deuterium. In the spectrum of **1b**, one proton signal at δ 3.56 ppm disappeared, and double doublet peaks centered at δ 3.65 ppm changed to the broad doublet at δ 3.64 ppm. These results also confirmed that the H1*proR* was selectively replaced by a deuterium. The partially relaxed ^1H -NMR spectra (180– t –90 pulse with internal times (t)=1300 msec) were successfully applied to separate the signals of a methin proton at C-1 from one of the overlapping H-3 signals, and thereby to characterize more precisely the two isomers **1a** and **1b**. In the same way, the two isomeric tripalmitins derived from **1a** and **1b** were also characterized (Fig. 2).

Fig. 3. 100 MHz ^{13}C -NMR Spectra (Complete Proton Decoupling) of Glycerol, **1a** and **1b** in D_2O .

In Fig. 3, the ^{13}C -NMR spectra of **1a**, **1b** and glycerol in D_2O are compared. A significant change in the intensity of the peak (C-1 and C-3) at δ 65.3 ppm and the appearance of new triplet signals at δ 65.0 ppm confirmed that the C-1 position in **1a** and **1b** was mono-deuteriated. The chemical shifts of C-1, C-2 and C-3 showed little difference between **1a** and **1b** to characterize their stereochemistry (Table I), and similar results were obtained for the tripalmitins (Fig. 4).

The isotope shifts in the ^{13}C -NMR spectra of **1a**, **1b** and the tripalmitins are also summarized in Table 1. The isotope shift was observed in the order of the magnitude of as C-1 > C-2 > C-3 for **1a** and **1b**, as well as for the two deuteriated tripalmitins. The isotope shift has been suggested to change due to the spacial distance from the deuterium or to the linearity with the C- ^2H axis.^{12,13} We could, therefore

Table I. ^{13}C -NMR ISOTOPE SHIFTS IN *sn*-GLYCEROLS AND TRIPALMITINS CHIRALLY DEUTERATED AT THE C-1 POSITION

Compound	Solvent	δ Chemical shift (ppm) ^{a,b}		
		C1 (ΔC1)	C2 (ΔC2)	C3 (ΔC3) ^c
Glycerol	D_2O	65.34 (0.0)	74.92 (0.0)	65.34 (0.0)
(1 <i>S</i>)-[1- ^2H] Glycerol	D_2O	64.99 (−0.35)	74.85 (−0.07)	65.31 (−0.03)
(1 <i>R</i>)-[1- ^2H] Glycerol	D_2O	64.99 (−0.35)	74.85 (−0.07)	65.33 (−0.01)
Tripalmitin	CDCl_3	62.08 (0.0)	68.83 (0.0)	62.08 (0.0)
(1 <i>S</i>)-[1- ^2H] Tripalmitin	CDCl_3	61.79 (−0.29)	68.78 (−0.05)	62.07 (−0.01)
(1 <i>R</i>)-[1- ^2H] Tripalmitin	CDCl_3	61.79 (−0.29)	68.78 (−0.05)	62.07 (−0.01)

^a Measured at 100 MHz in the completely ^1H decoupled mode with resolution at ± 0.015 ppm.

^b Referred to the internal 3-(trimethylsilyl)propane-sulfonic acid sodium salt (0.000 ppm) for the glycerols and to CDCl_3 (77.000 ppm) for the tripalmitins.

^c Difference in the chemical shifts between the deuteriated and non-deuteriated analogues.

Ex. $\Delta\text{C1} = \text{C1 (deuteriated derivative)} - \text{C1 (nondeuteriated analogue)}$.

Fig. 4. 100 MHz ^{13}C -NMR Spectra (Complete Proton Decoupling) of Tripalmitin and Its (1S)- and (1R)-Deuteriated Analogues in CDCl_3 .

Fig. 5. Three Rotamers about the C1-C2 (ϕ_1) Bond, *gg*, *gt* and *tg*.

gg calls for a conformation where the C1-O1 axis is *gauche* to both of the C2-O2 and C2-C3 axes, *gt* calls for a conformation where the C1-O1 axis is *gauche* to the C2-O2 and *trans* to the C2-C3, and *tg* calls for a conformation where the C1-O1 axis is *trans* to the C2-O2 and *gauche* to the C2-C3 axis.

Here, the conformation about the C2-C3 bond (ϕ_2) is not specified.

have expected some difference in the deuterium shift between **1a** and **1b** or the two deuteriated tripalmitins. In our experiments, however, the isotope shift for the ^{13}C signals showed little difference between the two sets of diastereomers. This may be ascribed to rotational averaging due to rapid rotation along the C1-C2 (ϕ_1 , Fig. 5) or C2-C3 bond (ϕ_2) in solution.

c) Complete assignments of the prochiral protons at C1 and C3 of *sn*-glycerides and conformational analyses

The ^1H -NMR spectra shown in Figs. 1 and 2 enabled us to assign all four prochiral protons at C1 and C3 of the glycerides, which has long been an unresolved problem in the conformational study of glycerolipids.³⁻⁷ This success is significant, because the two protons at C1 (or C3) were magnetically unequivalent to give separate signals, whose NMR parameters (vicinal coupling constants ($^3J_{\text{H,H}}$), chem-

Table II. 400 MHz ^1H -NMR DATA OF *sn*-GLYCEROL AND ITS TRI-*O*-ACYLATES

Compound		Chemical shift (ppm) ^a	Assingment	² <i>J</i> ^b (Hz)	³ <i>J</i> (Hz)	Population ^c (%)		
						<i>gg</i>	<i>gt</i>	<i>tg</i>
R =	3.652	H1 <i>S</i> , H3 <i>R</i>	11.7	4.2	33	52	15
	H	3.557	H1 <i>R</i> , H3 <i>S</i>	11.7	6.6			
	(D ₂ O)	3.780	H2					
	Pal	4.294	H1 <i>S</i> , H3 <i>R</i>	11.7	4.4	37	45	18
	(CDCl ₃)	4.145	H1 <i>R</i> , H3 <i>S</i>	11.7	6.0			
		5.267	H2					
	Ac	4.299	H1 <i>S</i> , H3 <i>R</i>	12.1	4.4	39	43	18
	(CDCl ₃)	4.162	H1 <i>R</i> , H3 <i>S</i>	12.1	5.9			
		5.253	H2					
	Bz	4.755	H1 <i>S</i> , H3 <i>R</i>	12.1	4.4	39	43	18
	(CDCl ₃)	4.686	H1 <i>R</i> , H3 <i>S</i>	12.1	5.8			
		5.834	H2					

^a 3-(Trimethylsilyl)-propanesulfonic acid sodium salt as internal standard (0.000 ppm) for glycerol (R = H), and tetramethylsilane (TMS) as the internal standard (0.000 ppm) for its tri-*O*-acylates (Ac, Bz, Pal).

^b Observed first order couplings ± 0.2 Hz.

^c Calculated from the following equations based on the Karplus equation of Haasnoot *et al.* (refs. 14, 19 and 20).

$$2.8\,gg + 3.1\,gt + 10.7\,tg = J_{\text{H1S}, \text{H2}} \quad (1)$$

$$0.9\,gg + 10.7\,gt + 5.0\,tg = J_{\text{H1R}, \text{H2}} \quad (2)$$

$$gg + gt + tg = 1 \quad (3)$$

ical shifts and relaxation rates) would provide key information for the conformation in solution.⁴⁻⁷⁾ The complete assignment of the four prochiral protons (H1*proR*, H1*proS*, H3*proR* and H3*proS*) of *sn*-glycerol and tri-*O*-acylated glycerides are summarized in Table II, where the rotameric distribution of the three staggered conformers, namely *gt*, *gg* and *tg* (Fig. 5) calculated from the vicinal coupling constants with H2,^{6,7)} are also given. The significant points could be summarized as follows: (1) H1*proR* (or H3*proS*) showed higher field shifts and larger coupling constants with H-2 than did H1*proS* (or H3*proR*), and (2) the two *gauche* conformers *gg* and *gt* predominated in which *gt* was more favored. The preference of the two *gauche* conformers (*gg* and *gt*) agreed with the results for phospholipids by Hauser *et al.*^{6,7)} as consistent with the *gauche* effect^{15,16)} which has been well accepted for carbohydrate molecules with acyclic C5-C6 bonds.^{17,18)} These results will become an important basis for further conformational analyses of glycerolipids by NMR spectroscopy.

Experimental

IR spectra were recorded on a Jasco A-202 spectrometer in liquid film form on a KBr plate. ^1H -NMR spectra were recorded with a JEOL FX-100 spectrometer, and optical rotation was measured on a Jasco J-20 spectrometer at a 589 nm wavelength. Kiesel gel 60 GF₂₅₄ (Merck) was used for both analytical and preparative TLC.

(1*S*)-(1-²H)-1,2-*O*-(2-Hydroxyethylidene)-*sn*-glycerol (3). A mixture of (6*S*)-(6-²H)-1,6-anhydro- β -D-galactopyranose (2,¹⁰⁾ 500 mg) and NaIO₄ (1.6 g) in water (50 ml) was stirred for 1 hr at room temperature, neutralized with 0.1 M barium hydroxide solution, and then filtered with a pad of celite. The filtrate was poured into an NaBH₄ (300 mg)-ethanol (10 ml) mixture, and the solution was stirred for 3 hr. After the excess NaBH₄ had been decomposed with acetic acid, the mixture was concentrated to dryness. The residue was treated with a pyridine (50 ml)-acetic anhydride (10 ml) mixture for 12 hr. The solution was repeatedly concentrated *in vacuo* with an ethanol-toluene mixture, and the residue was chromatographed on SiO₂ in 30:1 toluene-ethyl acetate to give a syrupy (1*S*)-(1-²H)-1,2-*O*-(2-acetoxyethylidene)-3-*O*-acetyl-*sn*-glycerol (500 mg, 77%). $[\alpha]_D^{25} -5.5^\circ$ (0.6, CHCl₃). ^1H -NMR (CDCl₃, TMS): 2.10 (3H, s, -OCOCH₃), 2.11 (3H, s, OCOCH₃), 3.82 (1H, broad d, 4.9 Hz, H-1), 4.1~4.3 (4H, m, H-2a' + H-2b' + H-3a' + H-3b'), 4.2~4.44 (1H, m, H-2), 5.16 (1H, t, 3.8 Hz, H-1). IR cm^{-1} : 2920, 2850, 1730, 1430, 1362, 1220, 1140, 1040,

930, 860, 600.

A mixture of sodium (*ca.* 5 mg) and this syrup (100 mg) in dry methanol (10 ml) was stirred for 3 hr, neutralized with Amberlite IR-120 resin (H^+ form), filtered to remove the resin and concentrated to give a syrupy **3** (60 mg, 98%). $[\alpha]_D + 3.2^\circ$ (*c* 1.9, MeOH). IR $\nu_{cm^{-1}}$: 3360 (OH), 1620, 1140, 1040. 1H -NMR (D_2O , DSS): 3.5~3.8 (4H, H-2a' + H-2b' + H-3a + H-3b), 3.82 (1H, broad d, 5.6 Hz, H1*proR*), 4.30 (1H, m, H-2), 5.06 (1H, t, 2.9 Hz, H-1').

(1*S*)-(1- 2H)-*sn*-Glycerol (**1a**). Crude **3** dissolved in 60% trifluoroacetic acid (TFA) was kept at 60°C for 12 hr and concentrated *in vacuo*. The syrupy residue was treated with a pyridine (2 ml)-acetic anhydride (0.5 ml) mixture for 12 hr. The mixture was concentrated, and chromatographed on SiO_2 in benzene-ethyl acetate (3:1) to give a syrupy (1*S*)-(1- 2H)-tri-*O*-acetyl-*sn*-glyceride. Deacetylation of this compound in cat. NaOMe-MeOH in the same way as that for the preparation of **3** gave **1a** (30 mg, 80% yield from **2**).

(1*S*)-(1- 2H)-1,2-*O*-(2-*O*-Benzyloxyethylidene)-3-*O*-benzyl-*sn*-glycerol (**4**). A mixture of **3** (150 mg), NaH (110 mg) and benzyl bromide (470 mg) in dimethylformamide (10 ml) was stirred for 2 hr. The excess NaH was decomposed with small amount of methanol, and the solution was concentrated *in vacuo*. The residual syrup was diluted in 20 ml of $CHCl_3$, washed with water, dried over $MgSO_4$, and concentrated. The residual syrup was chromatographed on SiO_2 in *n*-hexane-benzene-ethyl acetate (10:1:1) to give **4** (320 mg, 91%). $[\alpha]_D + 15.4^\circ$ (*c* 0.5, $CHCl_3$). IR $\nu_{cm^{-1}}$: 2850, 1490, 1445, 1360, 1244, 1204, 1100, 738, 695, 602. 1H -NMR ($CDCl_3$, TMS): 3.3~3.7 (4H, m, H-3a + H-3b + H-2a' + H-2b'), 3.82 (1H, broad d, 5.8 Hz, H-1*S*), 4.25 (1H, m, H-2), 4.54 (2H, s, $-CH_2$ -Ph), 4.59 (2H, s, $-CH_2$ -Ph), 5.10 (1H, t, 3.9 Hz).

(1*S*)-(1- 2H)-3-*O*-Benzyl-*sn*-glycerol (**5**). A solution of **4** (200 mg) in 60% TFA was kept at 60~65°C for 24 hr and concentrated *in vacuo*. The residual syrup was chromatographed on SiO_2 in chloroform-MeOH (100:1) to afford syrupy **5** (80 mg, 68%). $[\alpha]_D + 16^\circ$ (*c* 0.16, MeOH). 1H -NMR (D_2O , DSS): 3.3~3.8 (3H, H1*proR* + H-3a + H-3b), 3.89 (1H, m, H-2), 4.52 (2H, s, CH_2 -Ph), 4.85 (2H, s, 2 × DOH), 7.36 (5H, s, $-C_6H_5$).

(1*S*)-(1- 2H)-1-*O*- 1 Butyldimethylsilyl-3-*O*-benzyl-*sn*-glycerol (**6**). To a mixture of **5** (120 mg), triethylamine (120 mg) and 4-(*N,N*-dimethylamino)pyridine (20 mg) in CH_2Cl_2 (10 ml) was added 1 butyldimethylsilylchloride (240 mg). The mixture was stirred at room temperature for 6 hr, washed with water and dried over $MgSO_4$. The solution was concentrated to give a syrupy residue, which was chromatographed on SiO_2 in *n*-hexane-ethyl acetate (50:1) to afford **6** (167 mg, 85%), $[\alpha]_D + 11.5^\circ$ (*c* 0.3, $CHCl_3$). IR $\nu_{cm^{-1}}$: 3450, 2920, 2850, 1460, 1250, 1090, 835, 772, 730, 695. 1H -NMR ($CDCl_3$, TMS): 0.04 (6H, s,

$-Si(CH_3)_2$), 0.86 (9H, s, $-Si^tBu$), 2.44 (1H, d, 4.9 Hz, OH-2), 3.5~3.8 (3H, H1*proR* + H-3a + H-3b), 3.8 (1H, m, H-2), 4.52 (2H, s, $-CH_2$ -Ph), 7.30 (5H, s, $-C_6H_5$).

(1*S*)-(1- 2H)-2,3-di-*O*-Benzyl-*sn*-glycerol (**8**). A mixture of **6** (100 mg), NaH (20 mg) and benzylbromide (100 mg) in dimethylformamide (10 ml) was stirred for 3 hr at room temperature. After the excess NaH had been decomposed with methanol, the mixture was diluted with $CHCl_3$ (30 ml), washed with water, dried over $MgSO_4$ and concentrated *in vacuo*. The residual syrup was dissolved in 1 M *n*-Bu $_4$ NF in a tetrahydrofuran solution (2 ml), and the mixture was refluxed for 3 hr. The solution was diluted with 50 ml of ethyl acetate, washed with a sat. NaCl aqueous solution, dried over Na_2SO_4 and concentrated *in vacuo*. The residual syrup was chromatographed on SiO_2 in benzene-ethyl acetate (5:1) to give a syrupy **8** (80 mg, 87%). $[\alpha]_D + 21.8^\circ$ (*c* 0.22, $CHCl_3$). IR $\nu_{cm^{-1}}$: 3400 (OH), 2920, 2850 (CH), 738 (Bn), 698 (Bn).

(1*R*)-(1- 2H)-1-*O*-Benzoyl-2,3-di-*O*-benzyl-*sn*-glycerol (**10**). To a stirred solution of **8** (70 mg) in pyridine (15 ml) was added dropwise methanesulfonyl chloride (0.1 ml). The mixture was stirred for 0.5 hr and poured into an ice-water mixture (10 ml). The mixture was extracted with chloroform (3 × 10 ml), before the combined extract was washed with water, sat. $NaHCO_3$ and water, and dried over $MgSO_4$. Analytical TLC (silica gel, ethyl acetate-benzene = 1:10) for the dried solution showed the complete disappearance of **8** (*Rf* = 0.1) and the appearance of new single spot of a 1-*O*-mesylated compound (**9**, *Rf* = 0.3). Concentration of the solution gave a syrupy residue, which was purified through a short silica gel column in benzene-ethyl acetate (20:1). A mixture of **9** and sodium benzoate (100 mg) in dimethylformamide (10 ml) was stirred at 120°C for 6 hr. After the mixture had been cooled to room temperature, a sat. NaCl aqueous solution (20 ml) was added, and the solution was extracted with ethyl acetate (10 ml × 3). The combined extract was washed with a sat. NaCl aqueous solution, dried over Na_2SO_4 and concentrated. The residual syrup was chromatographed on a silica gel column in *n*-hexane-ethyl acetate (10:1) to afford a syrupy **10** (78 mg, 80% from **10**). $[\alpha]_D - 16.7^\circ$ (*c* 0.1, MeOH). IR $\nu_{cm^{-1}}$: 1720 ($-O-CO-Ph$), 1600, 1450, 1270, 1100, 735, 710, 695. 1H -NMR ($CDCl_3$, TMS): 3.66 (2H, H-3 + H-3'), (2H, H-3 + H-3'), 4.00 (1H, m, H-2), 4.51 (1H, d, H-1*S*), 4.57 (2H, s, $-CH_2$ -Ph), 4.72 (2H, s, $-CH_2$ -Ph), 7.3~7.6 (13H, m, 2 × Ph (5H) and benzoyl protons at *meta* (2H) and *para* (1H) positions), 8.01 (2H, dd, benzoyl protons at *ortho* positions (2H)).

(1*R*)-(1- 2H)-*sn*-Glycerol (**1b**). A mixture of **10** (70 mg) and Na (*ca.* 2 mg) in MeOH (10 ml) was heated at 55°C for 2 hr, neutralized with Amberlite IR-120 resin (H^+ form) and concentrated. The residue was chromatographed on SiO_2 in *n*-hexane-ethyl acetate (10:1) to give a syrupy (1*R*)-isomer of **8** (48 mg, 95%). The syrup (48 mg) was dissolved in MeOH and hydrogenated with Pd-black

(100 mg) at room temperature. The catalyst was removed by filtration, and the filtrate was evaporated to dryness to afford a syrupy **1b** (11 mg, 72% from **10**).

References and Notes

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