NOTES

# The synthesis of L-mycarose and L-cladinose

G. B. HOWARTH AND J. K. N. JONES

The syntheses of the title compounds were first achieved by a procedure based on non-carbohydrate precursors, and resulted in racemic compounds (1), necessitating an optical resolution to obtain the optically active isomers.

The syntheses of the D-isomers were recently achieved in this laboratory (2) by a route involving the introduction of a branch into a hexose derivative; syntheses by a similar procedure were reported at about the same time by Overend *et al.* (3). This note reports the syntheses of the naturally occurring L-enantiomers by a route identical with that used by us for the D-isomers (2).

Methyl 4,6-*O*-benzylidene-2-deoxy-α-L-*arabino*-hexoside was obtained by standard procedures from 2-deoxy-L-*arabino*-hexose (4), which, on oxidation with ruthenium tetroxide, gave methyl 4,6-*O*-benzylidene-2-deoxy-α-L-*erythro*-hexopyran-3-uloside. Branching was introduced at C-3 by treatment of the ketone with methylmagnesium iodide. The benzylidene group was removed by catalytic hydrogenation, and the product was selectively tosylated at the primary position to give methyl 2-deoxy-3-*C*-methyl-6-*O*-*p*-toluenesulfonyl-α-L-*ribo*-hexopyranoside. The 6-*O*-tosyl compound was converted directly into the 6-deoxy derivative by reduction with lithium aluminium hydride in tetrahydrofuran. The glycosidic group was removed by mild acid hydrolysis to give a compound whose physical constants were in good agreement with those previously reported for L-mycarose (1, 5, 6). The infrared and nuclear magnetic resonance spectra were identical with those described for L-mycarose (7).

L-Cladinose was obtained from the intermediate methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-L-*ribo*-hexopyranoside, which was methylated to give the 3-*O*-methyl ether and converted into the sugar by the route described for L-mycarose. A compound was obtained whose physical constants and infrared spectrum were in good agreement with those reported for L-cladinose (1, 8). The compound was further characterized by conversion into a crystalline 1,4-di-*O*-acetate.

It is pertinent to point out the advantages of the route employed in this note over that described by Overend *et al.* (3) for the syntheses of the D-enantiomers.

Branching was effectively introduced into methyl 4,6-*O*-benzylidene-2-deoxy-α-L-*erythro*-hexopyrano-3-riboside by the addition of the ketone dissolved in benzene to a solution of the Grignard reagent in ether. Overend *et al.* report having some experimental difficulty in causing the reagent to react with the ketone (3). Both methyl 2-deoxy-3-*C*-methyl-6-*O*-*p*-toluenesulfonyl-α-L-*ribo*-hexopyranoside and methyl 2-deoxy-3-*C*-methyl-3-*O*-methyl-6-*O*-*p*-toluenesulfonyl-α-L-*ribo*-hexopyranoside were converted directly into the 6-deoxy derivatives by treatment with lithium aluminium hydride in tetrahydrofuran. Overend *et al.*, however, obtained the deoxy derivatives of the above two compounds in the D-series by the more lengthy procedure involving the preparation of the intermediate 6-iodo derivatives (3). Although Overend *et al.* were unsuccessful in attempts to methylate methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside with dimethyl sulfate, we obtained excellent etherification of the corresponding L-isomer

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when the above reagent was employed in tetrahydrofuran in the presence of solid sodium hydroxide.

## EXPERIMENTAL

Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Bendix automatic polarimeter (type 143A) at a temperature of 20 ± 2°. Infrared absorption spectra were measured on a Beckman model IR5A spectrophotometer as Nujol mulls, unless otherwise stated. Nuclear magnetic resonance spectra were determined at 60 mc/s with a Varian A-60 spectrometer. Paper chromatography was carried out by the descending method on Whatman No. 1 filter paper, with butan-1-ol saturated with water as solvent. The sugars were detected by spraying the chromatograms with a mixture of equal volumes of vanillin (1% solution in ethanol) and perchloric acid (3% solution in water) and heating them for 2 min.

### *Methyl 4,6-O-Benzylidene-2-deoxy-α-L-erythro-hexopyranoside*

Methyl 2-deoxy-α-L-*arabino*-hexopyranoside (6 g) (9) was stirred with benzaldehyde (30 ml) and zinc chloride (6 g) overnight. The benzylidene derivative was isolated in the usual manner and recrystallized from ether–petrol (5.4 g, 60%), m.p. 152–53°, $[\alpha]_D$ −90° (*c*, 0.8 in ethanol). Literature values for the D-isomer are m.p. 151–152° and $[\alpha]_D$ +90° (*c*, 1.0 in acetone) (3).

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.1; H, 6.7. Found: C, 62.9; H, 6.5.

### *Methyl 4,6-O-Benzylidene-2-deoxy-α-L-erythro-hexopyrano-3-uloside*

Methyl 4,6-*O*-benzylidene-2-deoxy-α-L-*arabino*-hexopyranoside (5.4 g) was oxidized to the 3-*keto* compound by the dropwise addition of saturated sodium metaperiodate solution to its solution in chloroform containing ruthenium dioxide (200 mg) (10). The ketone was isolated as a crystalline compound (2.7 g, 51%), m.p. 176–177°, $[\alpha]_D$ −150° (*c*, 0.3 in ethanol). Literature values for the D-isomer are m.p. 177–178° and $[\alpha]_D$ +159° (*c*, 0.2 in ethyl acetate) (3). The infrared spectrum showed absorption at 5.8 μ (C=O) and 13.4 and 14.4 μ (Ph).

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.6; H, 6.1. Found: C, 63.9; H, 5.8.

### *Methyl 4,6-O-Benzylidene-2-deoxy-3-C-methyl-α-L-ribo-hexopyranoside*

Methyl 4,6-*O*-benzylidene-2-deoxy-α-L-*erythro*-hexopyrano-3-uloside (1.33 g) was dissolved in dry benzene, and the solution was added dropwise to excess methylmagnesium iodide in ether at 0°. After the reaction mixture was left at room temperature for 1 h, it was decomposed by pouring it into water; then the product was isolated. After recrystallization from ether–petrol, the product[1] (0.81 g, 59%) had m.p. 94–95° and showed $[\alpha]_D$ −120° (*c*, 0.3 in ethanol). Literature values for the D-isomer are m.p. 125.5–126° and $[\alpha]_D$ +121° (*c*, 0.2 in ethanol) (3), and m.p. 93–94° and $[\alpha]_D$ +119° (*c*, 0.9 in ethanol) (2). The infrared spectrum showed absorption at 2.85 μ (OH) and 14.4 μ (Ph), but none at 5.8 μ (C=O).

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.3; H, 7.4. Found: C, 64.3; H, 7.4.

### *Methyl 2-Deoxy-3-C-methyl-α-L-ribo-hexopyranoside*

The 4,6-*O*-benzylidene derivative (650 mg) was dissolved in ethanol (20 ml) and hydrogenated at atmospheric pressure in the presence of 10% palladium on carbon. The catalyst was removed by filtration and the solution evaporated to yield a syrup (428 mg, 94%), $[\alpha]_D$ −154° (*c*, 0.8 in ethanol). Literature values for the D-isomer are m.p. 58.5–59° and $[\alpha]_D$ +156° (*c*, 0.7 in ethanol) (3). The infrared spectrum showed absorption at 2.85 μ (OH), but none at 13.4 or 14.4 μ (Ph) (liquid film).

### *Methyl 2-Deoxy-3-C-methyl-6-O-p-toluenesulfonyl-α-L-ribo-hexopyranoside*

Methyl 2-deoxy-3-*C*-methyl-α-L-*ribo*-hexopyranoside (410 mg) was treated with *p*-toluenesulfonyl chloride (500 mg, 1.25 moles) in dry pyridine (3 ml) at 0°. After the mixture was left at room temperature for 24 h, it consisted of mono- and di-*O*-tosyl derivatives and unchanged starting material. Then it was poured into water (50 ml) and extracted with chloroform. Evaporation of the extracts after they had been washed with sulfuric acid (2 *N*) and water yielded a viscous syrup, which was chromatographed on silica gel, with ethyl acetate – petrol (30:70 v/v) as eluent. The 6-*O*-tosyl derivative was isolated as fine needles after recrystallization from chloroform–petrol (430 mg, 58%), m.p. 106–107°, $[\alpha]_D$ −94° (*c*, 0.5 in ethanol). Literature values for the D-isomer are m.p. 85–85.5° and $[\alpha]_D$ +94° (*c*, 1.0 in chloroform) (3), and m.p. 106–107° and $[\alpha]_D$ +95° (*c*, 0.6 in ethanol) (2). The infrared spectrum showed absorption at 2.83 and 2.9 μ (OH), 6.25 μ (Ph), and 7.4 and 8.48 μ (S=O).

Anal. Calcd. for $C_{15}H_{22}O_7S$: C, 52.0; H, 6.4; S, 9.0. Found: C, 52.0; H, 6.4; S, 9.1.

### *Methyl 2,6-Dideoxy-3-C-methyl-α-L-ribo-hexopyranoside (Methyl α-L-Mycaroside)*

The 6-*O*-tosyl derivative (400 mg) was heated under reflux with lithium aluminium hydride in tetrahydrofuran for 1 h. Fractionation of the resulting mixture of compounds on silica gel, with ethyl acetate – petrol (40:60 v/v) as eluent, gave the 2,6-dideoxy compound (150 mg, 75%), m.p. 55–57°, $[\alpha]_D$ −143° (*c*, 0.7 in ethanol). Literature values for the L-isomer are m.p. 60.5–61° and $[\alpha]_D$ −141° (*c*, 1 in chloroform) (5), and for the D-isomer are m.p. 56–57° and $[\alpha]_D$ +136° (*c*, 1.0 in chloroform) (3).

### *2,6-Dideoxy-3-C-methyl-α-L-ribo-hexose (L-Mycarose)*

Methyl α-L-mycaroside (150 mg) was kept in 0.6 *N* hydrochloric acid for 24 h. The solution was neutralized and, on evaporation, yielded the crystalline free sugar, which was recrystallized from ethyl

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[1] In the D-series, this compound was found to exist in two crystalline modifications, m.p. 94–95° and 125–126° (2).

acetate – petrol (80 mg, 58%), m.p. 116–118°. Vacuum sublimation of this material (bath temperature 110–115° at 0.005 mm) gave pure L-mycarose as fine needles, m.p. 127–128°, $[\alpha]_D$ −32° (*c*, 0.6 in water). Literature values are m.p. 128–129° and $[\alpha]_D$ −31.1° (*c*, 4 in water) (5), m.p. 128.5–130.5° (1), and m.p. 132–134° and $[\alpha]_D$ −31° (*c*, 4 in water) (6).

Its infrared and nuclear magnetic resonance spectrographic properties were the same as those previously reported for L-mycarose (7). The material was examined by paper chromatography, and showed one component as a deep-blue spot whose mobility was identical with that reported for D-mycarose ($R_f$ 0.63) (3).

### *1,4-Di-O-acetyl-3-C-methyl-α-L-ribo-hexose*

L-Mycarose (32 mg) was heated with a mixture of pyridine (2 ml) and acetic anhydride (0.25 ml) at 100° for 1 h. The acetate was isolated in the normal manner as a syrup, which crystallized from ether–petrol (18 mg, 39%), m.p. 88–90°.

Anal. Calcd. for $C_{11}H_{18}O_6$: C, 53.6; H, 7.3. Found: C, 53.5; H, 7.3.

### *Methyl 4,6-O-Benzylidene-2-deoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranoside*

Methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-L-*ribo*-hexopyranoside (2.1 g) was methylated at the tertiary hydroxyl group by the dropwise addition of dimethyl sulfate (25 ml) to its solution in tetrahydrofuran (40 ml) containing finely powdered sodium hydroxide (5 g). The methyl ether was isolated and recrystallized from petrol (b.p. 100–120°) to give the pure product (2 g, 90%), m.p. 105–106°, $[\alpha]_D$ −117° (*c*, 0.6 in ethanol). Literature values for the D-isomer are m.p. 106.5–107° and $[\alpha]_D$ +119° (*c*, 1.2 in ethanol) (3). The infrared spectrum showed absorption at 13.4 and 1.44 μ (Ph), but none in the 2.8–2.9 μ region (OH).

Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.3; H, 7.5. Found: C, 65.2; H, 7.6.

### *Methyl 2-Deoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranoside*

Methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranoside (2 g) was dissolved in ethanol (25 ml) and hydrogenated in the presence of 10% palladium on carbon at atmospheric pressure. The catalyst was removed by filtration and the solution evaporated to yield the impure product as a syrup, which was purified by fractionation on a column of silica gel, with ethyl acetate – petrol (30:70 v/v) as eluent. A syrupy product was obtained (1.3 g, 93%), $[\alpha]_D$ −147° (*c*, 0.5 in ethanol). The literature value for the D-isomer is $[\alpha]_D$ +148° (*c*, 0.8 in ethanol) (3). The infrared spectrum showed absorption at 2.9 μ (OH), but none at 13.4 or 14.4 μ (Ph).

### *The Mono- and Di-O-tosyl Derivatives of Methyl 2-Deoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranoside*

Syrupy methyl 2-deoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranoside (1.3 g) was treated with *p*-toluenesulfonyl chloride (1.8 g, 1.75 moles) in dry pyridine (10 ml) at 0°. After the reaction mixture was left at room temperature for 24 h, it contained the mono- and di-*O*-tosyl derivatives and a small amount of unchanged starting material. The solution was poured into water (100 ml) and the products were extracted with chloroform. Evaporation of the chloroform extracts after they had been washed with sulfuric acid (2 *N*) and water yielded a viscous syrup, which was chromatographed on silica gel, with ethyl acetate – petrol (30:70 v/v) as eluent. The 4,6-di-*O*-tosyl derivative was obtained as large prisms after recrystallization from ethyl acetate – petrol (0.5 g), m.p. 124–125°, $[\alpha]_D$ −107° (*c*, 0.5 in ethanol). Literature values for the D-isomer are m.p. 125.5–126° and $[\alpha]_D$ +108° (*c*, 0.4 in ethanol) (3). The infrared spectrum showed absorption at 6.25 μ (Ph) and 7.4 and 8.48 μ (S=O).

Anal. Calcd. for $C_{23}H_{30}O_9S_2$: C, 53.7; H, 5.9. Found: C, 53.8; H, 6.1.

The mono-*O*-tosyl derivative was isolated as a syrup (1.1 g, 49%), $[\alpha]_D$ −101° (*c*, 0.6 in ethanol). The literature value for the D-isomer is $[\alpha]_D$ +103° (*c*, 0.5 in ethanol) (3). The infrared spectrum showed absorption at 2.85 μ (OH), 6.25 μ (Ph), and 7.4 and 8.48 μ (S=O) (liquid film).

Anal. Calcd. for $C_{16}H_{24}O_7S$: C, 53.3; H, 6.7. Found: C, 53.1; H, 6.4.

### *Methyl 2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranoside*

The 6-*O*-tosyl derivative (1.0 g) was heated under reflux with lithium aluminium hydride (0.5 g) in tetrahydrofuran (25 ml) for 1 h. Fractionation of the resulting mixture of compounds on silica gel, with ethyl acetate – petrol (40:60 v/v) as eluent, gave the 2,6-dideoxy derivative as a mobile liquid (380 mg, 72%), $[\alpha]_D$ −7° (*c*, 3.5 in water). The literature value for the L-isomer is $[\alpha]_D$ −6.9° (*c*, 3 in water) (8), and those for the D-isomer are m.p. 27.5–28.5° and $[\alpha]_D$ +7.3° (*c*, 4.1 in water) (3).

### *2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexose (D-Cladinose)*

Methyl α-L-cladinoside (350 mg) was dissolved in 0.6 *N* hydrochloric acid and kept at room temperature for 48 h. The solution was neutralized and evaporated to give the crude free sugar as a syrup (312 mg). Purification was achieved by chromatography on silica gel, with diethyl ether as eluent, followed by distillation, to give pure L-cladinose (290 mg, 89%), b.p. 90–100° at 0.05 mm, $[\alpha]_D$ −24° (*c*, 1.3 in water). Literature values are b.p. 120–132° at 0.25 mm and $[\alpha]_D$ −23° (*c*, 2.6 in water) (8).

Anal. Calcd. for $C_8H_{16}O_4$: C, 54.5; H, 9.1. Found: C, 54.5; H, 9.1.

Its infrared spectrum (chloroform solution) was identical with that described for L-cladinose (1). The material was analyzed by paper chromatography and showed one component as a deep-blue spot ($R_f$ 0.78). The literature value for the D-isomer is $R_f$ 0.76 (3).

### *1,4-Di-O-acetyl-3-C-methyl-3-O-methyl-α-L-ribo-hexose*

D-Cladinose (94 mg) in dry pyridine (4 ml) was heated with freshly distilled acetic anhydride

(0.5 ml) at 90° for 2 h. The acetate was isolated in the usual manner as a syrup, which crystallized from pentane (56 mg, 40%), m.p. 65–66°, $[\alpha]_D$ −38° (*c*, 0.6 in methanol). Literature values are m.p. 66–67° and $[\alpha]_D$ −36° (*c*, 1.4 in methanol) (11).

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 55.4; H, 7.7. Found: C, 55.0; H, 8.0.

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DEPARTMENT OF CHEMISTRY,
QUEEN'S UNIVERSITY,
KINGSTON, ONTARIO.

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# Rearrangement studies with $^{14}C$. XXX. The demercuration of 2-phenyl-1-$^{14}C$-ethylmercuric perchlorate

C. C. LEE AND R. J. TEWARI

The solvolyses of 2-phenyl-1-$^{14}C$-ethyl tosylate in different solvents gave various amounts of isotope position rearrangements (1–3). However, the lack of significant enhancements in the titrimetric rates in these solvolyses has added to the debate on nonclassical versus equilibrating classical ions (4, 5). Appreciable amounts of enhancement in the rates of acetolysis and formolysis of 2-phenylethylmercuric perchlorate have been observed, and the results were interpreted as evidence for phenyl participation in the rate-determining ionization (6). The present note reports the extents of rearrangement of the $^{14}C$ label from C-1 to C-2 in the solvolytic demercuration of 2-phenyl-1-$^{14}C$-ethylmercuric perchlorate (I-$HgClO_4$) in formic acid, acetic acid, and ethanol.

2-Phenyl-1-$^{14}C$-ethyl bromide (7) was converted into 2-phenyl-1-$^{14}C$-ethylmercuric acetate (I-HgOAc) by the procedures of Ouellette (8). Oxidation of this acetate gave inactive benzoic acid, indicating that all of the $^{14}C$ label was located at C-1. I-HgOAc and an equimolar quantity of perchloric acid (8–10) were subjected to solvolysis, at reflux temperature, in formic acid, acetic acid, or ethanol. The products that were recovered (2-phenylethyl formate, 2-phenylethyl acetate, or 2-phenylethyl ethyl ether, respectively) were oxidized to benzoic acid, the activity of which served as a measure of the extent of $^{14}C$ rearrangement from C-1 to C-2. The results are summarized in Table I.

From Table I, it is seen that about 7, 44, and 45% isotope position rearrangements have taken place in the demercuration of I-$HgClO_4$ in ethanol, acetic acid, and formic acid, respectively. The fact that the least rearrangement was observed in the most nucleophilic of these solvents (ethanol) is not unexpected. These data may be compared with the analogous values of about 0.3, 5, and 45% rearrangements found, respectively, in the ethanolysis, acetolysis, and formolysis of 2-phenyl-1-$^{14}C$-ethyl to-