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SYNTHESIS OF 1D- AND 1L-4-*O*-BENZYL-*myo*-INOSITOL, 1D-4-*O*-α-L-FUCOPYRANOSYL-*myo*-INOSITOL (IDENTICAL TO A NATURAL GLYCOSIDE), AND 1L-4-*O*-α-L-FUCOPYRANOSYL-*myo*-INOSITOL

PER J. GAREGG, BENGT LINDBERG,
Department of Organic Chemistry, Arrhenius Laboratory, University of Stockholm, S-106 91 Stockholm (Sweden)

INGEMAR KVARNSTRÖM, AND STEFAN C. T. SVENSSON
Department of Chemistry, University of Linköping, S-581 83 Linköping (Sweden)
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ABSTRACT

The α-L-fucopyranosyl-*myo*-inositol isolated from human urine has been proved to be the 1D-4-*O*-*myo*-inositol derivative by unambiguous syntheses of this substance and of the diastereomeric 1L-4-*O*-*myo*-inositol derivative. The chiral penta-*O*-benzoyl-*myo*-inositols used in the glycosidations, by the imidate method, were prepared from 1D- and 1L-4-*O*-benzyl-*myo*-inositol, respectively. The latter were resolved as the L(+)-*O*-acetylmandelates of the corresponding racemic 4-*O*-benzyl-1,6:2,3-di-*O*-cyclohexylidene-*myo*-inositol.

INTRODUCTION

Access to the six mono-*O*-benzyl-*myo*-inositols would be of value in structural studies of naturally occurring *myo*-inositol derivatives and in the synthesis of this class of substances. Various mono-*O*-benzyl-*myo*-inositols have been prepared by Angyal *et al.*[1,2] and two of the four chiral compounds, namely, the 1D- and 1L-benzyl ethers, by Shvets *et al.*[3,4]. We recently described improved syntheses of the two *meso* and the two racemic forms of mono-*O*-benzyl-*myo*-inositol[5]. We now report the synthesis of the enantiomeric 1D- and 1L-4-*O*-benzyl-*myo*-inositol and, *via* these ethers, of 1D- and 1L-4-*O*-α-L-fucopyranosyl-*myo*-inositol. By comparison with these glycosides, an α-L-fucopyranosyl-*myo*-inositol from human urine[6] was identified as the 1D-4-*O*-derivative.

RESULTS AND DISCUSSION

Racemic 4-*O*-benzyl-1,6:2,3-di-*O*-cyclohexylidene-*myo*-inositol[5] was esterified with L-(+)-*O*-acetylmandelic acid, and the resulting, diastereomeric mixture was resolved in high yield by chromatography on silica gel. Each of the dia-

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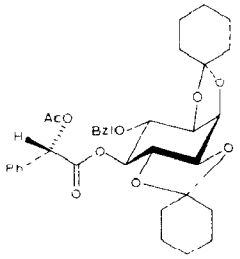
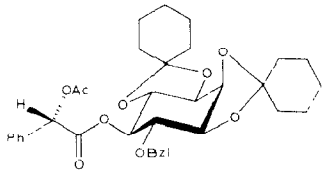
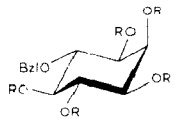
stereomers (**1a** and **1b**) was deacylated and then hydrolysed to give 1D- and 1L-4-*O*-benzyl-*myo*-inositol (**2a** and **2b**). The two enantiomers were identified by determining their specific optical rotations in cuprammonium solution (Cupra B) as devised by Reeves[7]. This method has previously been used for *myo*-inositol derivatives by Maehr *et al.*[8].



1a



1b



2a R = H (2b = enantiomer)
3a R = Bz (3b = enantiomer)

Each enantiomer should give three different complexes, each with 2 equiv. of cuprammonium (Table I). The sign of the shift in the molecular rotation, at 436 nm, on going from water to Cupra B depends upon the dihedral angle between the vicinal hydroxyl groups, and is $\sim\pm2000°$ when this angle is $\pm60°$, as determined for methyl glucopyranoside derivatives[7]. As seen from the data in Table I, a negative shift is expected for 1D-4-*O*-benzyl-*myo*-inositol and a corresponding positive shift for the 1L-4-*O*-isomer. The observed values ($-875°$ and $+925°$, respectively) are in reasonably good agreement with the values of $\pm1300°$ calculated on the assumption that each complex formation gives the same contribution to the shift and that the three bicuprammonium complexes are formed in equal amounts.

Benzoylation of **2a** and **2b** yielded the pentabenzoates **3a** and **3b**, respectively, which, on catalytic hydrogenation, yielded 1L- (**4a**) and 1D-1,2,3,4,5-penta-*O*-benzoyl-*myo*-inositol (**4b**), respectively. Glycosylation of these pentabenzoates with 2,3,4-tri-*O*-benzyl-1-*O*-(*N*-methylacetimidyl)-β-L-fucopyranose[9] yielded the protected α-L-fucopyranosides **5a** and **5b**. Deblocking by treatment with methanolic

TABLE I

COMPLEXES FORMED BETWEEN CUPRAMMONIUM AND 1D- AND 1L-4-*O*-BENZYL-*myo*-INOSITOL; ESTIMATED SIGN OF THE SHIFT IN THE MOLECULAR ROTATION FOR EACH COMPLEX AT 436 nm ON GOING FROM WATER TO CUPRA B AS SOLVENT

Substance	*Complex*	*Sign of shift*
1D-4-*O*-Benzyl-*myo*-inositol	1,2:5,6	+ −
	2,3:5,6	− −
	2,3,6,1	− +
1L-4-*O*-Benzyl-*myo*-inositol	1,2:3,4	+ −
	1,2:4,5	+ +
	2,3:4,5	− +

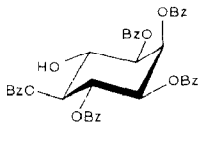
TABLE II

^{13}C-N M R. SPECTRA OF FUCOSYLINOSITOLS AND REFERENCE COMPOUNDS

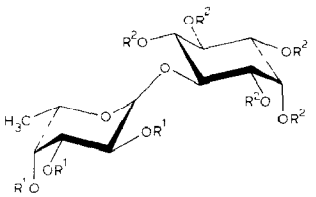
Compound	*Chemical shift*[a]											
	C-1'	*C-2'*	*C-3'*	*C-4'*	*C-5'*	*C-6'*	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
α-L-Fuc*p*-*myo*-inositol from urine	100.5	69.2	70.4	72.7	67.7	16.2	71.8	73.0	72.5	81.3	73.7	73.3
1D-4-*O*-α-L-Fuc*p*-*myo*-inositol (**6a**)	100.5	69.2	70.4	72.7	67.7	16.2	71.8	73.0	72.5	81.3	73.7	73.3
1L-4-*O*-α-L-Fuc*p*-*myo*-inositol (**6b**)	100.4	69.2	70.4	72.7	67.8	16.2	71.8	73.0	70.6	81.6	75.4	73.3
Methyl α-L-fucopyranoside[12]	100.4	68.9	70.6	72.8	67.4	16.6						
4-*O*-Benzyl-*myo*-inositol							71.8	73.2[b]	71.8	82.0	74.9[c]	73.3
myo-Inositol							71.9	73.0	71.9	73.2	75.1	73.2

[a]The δ-values, for aqueous solutions, with 1,4-dioxane at δ 67.405 *versus* external tetramethylsilane, are accurate to ±0.05 p.p.m. The assignments for 4-*O*-benzyl-*myo*-inositol were made by analogy with those for methyl-*myo*-inositols[13]. [b]Shift assignment by heteronuclear decoupling of H-2 only. [c]Shift assignment by heteronuclear decoupling of only CH_2Ph and H-5, respectively.

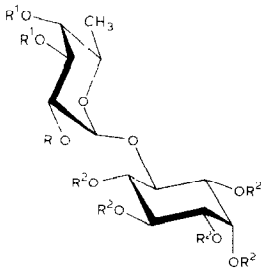
sodium methoxide followed by hydrogenation over palladium-on-carbon yielded the free glycosides 1D- (**6a**) and 1L-4-*O*-α-L-fucopyranosyl-*myo*-inositol (**6b**). The ^{13}C-n.m.r. spectrum of the α-L-fucopyranosyl-*myo*-inositol isolated from human urine[6] was indistinguishable from that of **6a** but clearly different from that of **6b** (Table II). As expected, the most significant differences were observed for the glycosyloxylated carbon atom and its two neighbours. The structure of the natural product is consequently 1D-4-*O*-α-L-fucopyranosyl-*myo*-inositol. Treatment of racemic 1,2,3,4,5-penta-*O*-benzoyl-*myo*-inositol with 2,3,4-tri-*O*-benzyl-1-*O*-(*N*-methylacetimidyl)-β-L-fucopyranose yielded a mixture of **5a** and **5b** which, however, could not be fractionated.



4a (**4b** = enantiomer)

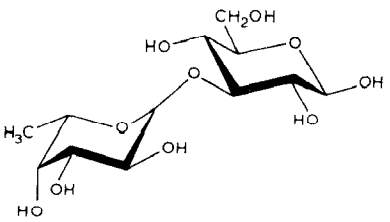


5a R^1 = Bzl, R^2 = Bz
6a R^1 = R^2 = H
≡ natural product



5b R^1 = Bzl, R^2 = Bz
6b R^1 = R^2 = H

Various glycosides of *myo*-inositol have been isolated from human urine and seem to be related to a group of oligosaccharides also present in the urine[10]. It has been proposed that *myo*-inositol replaces a reducing glucose residue present in these oligosaccharides. Some of these oligosaccharides contain an α-L-fucopyranosyl group linked to O-3 of this glucose residue, as in **7**. It is therefore not surprising that the steric environment of this α-L-fucopyranosyl group is similar in **6a** and **7**.



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EXPERIMENTAL

General methods. — These were the same as those previously reported[5]. ^{1}H- and ^{13}C-n.m.r. spectra were recorded for all substances. They were in agreement with the postulated structures and could, with few exceptions, be fully assigned

(the spectra are available from I. K. or S. C. T. S. upon request). Cuprammonium solution, Cupra B, was prepared as described by Reeves[7].

1D- (**1a**) *and 1L-5-O-L-(+)-O-acetylmandelyl-4-O-benzyl-1,6:2,3-di-O-cyclohexylidene-*myo*-inositol* (**1b**). — L-(+)-*O*-Acetylmandelic acid[11] (0.54 g, 2.7 mmol) in thionyl chloride (3 mL) was boiled under reflux for 3 h and the solution was then concentrated. The crude acid chloride was added dropwise at 0° to a stirred solution of racemic 4-*O*-benzyl-1,6:2,3-di-*O*-cyclohexylidene-*myo*-inositol (0.40 g, 0.93 mmol) in pyridine (10 mL). The solution was allowed to attain room temperature and, after 1 h, when reaction was complete (t.l.c.), it was diluted with dichloromethane, washed several times with water, dried ($MgSO_4$), filtered, and concentrated. Column chromatography on silica gel (chloroform–ethyl acetate, 60:1) gave **1b** (280 mg), $[\alpha]_D^{22}$ +24° (*c* 1, chloroform), R_F 0.77 (t.l.c., above solvent system); and **1a** (270 mg), m.p. 143–144° (from light petroleum–diethyl ether), $[\alpha]_D^{22}$ +35° (*c* 1, chloroform), R_F 0.66.

Anal. Calc. for $C_{35}H_{42}O_9$: C, 69.3; H, 6.98. Found: C, 69.2; H, 6.85.

*1D-4-O-Benzyl-*myo*-inositol* (**2a**). — Compound **1a** (250 mg) was treated with methanolic 0.15M sodium methoxide (10 mL) at room temperature for 2 h. The solution was neutralised with Dowex 50 (H^+) resin, filtered, and concentrated. A solution of the deacylated product in aqueous 80% acetic acid (8 mL) was boiled under reflux for 2 h, cooled, and concentrated. The crystalline product was purified by column chromatography (acetonitrile–water, 9:1) on silica gel to yield **2a** (96 mg, 86%), m.p. 175–177° (from methanol–2-propanol), $[\alpha]_D^{22}$ +6°, $[\alpha]_{436}^{22}$ +11° (*c* 1, methanol), $[\alpha]_{436}^{22}$ −313° (*c* 0.15, Cupra B).

Anal. Calc. for $C_{13}H_{18}O_6$: C, 57.8; H, 6.71. Found: C, 57.8; H, 6.74.

*1L-4-O-Benzyl-*myo*-inositol* (**2b**). — This compound was prepared from **1b** as described for **2a** and in comparable yield. It had m.p. 176–178°, $[\alpha]_D^{22}$ −6°, $[\alpha]_{436}^{22}$ −11° (*c* 1, methanol), and $[\alpha]_{436}^{22}$ +332° (*c* 0.15, Cupra B).

Anal. Calc. for $C_{13}H_{18}O_6$: C, 57.8; H, 6.71. Found: C, 57.6; H, 6.75.

The n.m.r. spectra of **2a** and **2b** were identical to those previously recorded for the racemic mixture[5].

*1L-1,2,3,4,5-Penta-O-benzoyl-6-O-benzyl-*myo*-inositol* (**3a**). — Benzoyl chloride (0.5 mL, 4.3 mmol) was added dropwise at room temperature to a stirred solution of **2a** (60 mg, 0.22 mmol) in pyridine (5 mL). The mixture was kept at 70° overnight, cooled, diluted with dichloromethane, washed with water, M hydrochloric acid, and water, dried ($MgSO_4$), filtered, and concentrated. The product was purified by column chromatography (chloroform–ethyl acetate, 50:1) on silica gel, to yield **3a** (166 mg, 96%), m.p. 212–214° (from light petroleum–diethyl ether), $[\alpha]_D^{22}$ −18° (*c* 1, chloroform).

*1D-1,2,3,4,5-Penta-O-benzoyl-6-O-benzyl-*myo*-inositol* (**3b**). — This compound was prepared from **2b** as described for **3a** and in comparable yield. It had m.p. 213–214°, $[\alpha]_D^{20}$ +18° (*c* 1, chloroform).

Racemic **3**, similarly obtained from **2**, had m.p. 182–183°.

Anal. Calc. for $C_{48}H_{38}O_{11}$: C, 72.9; H, 4.84. Found: C, 72.8; H, 4.90.

*1L-1,2,3,4,5-Penta-O-benzoyl-*myo*-inositol* (**4a**). — A solution of **3a** (135 mg) in tetrahydrofuran–ethanol (4:1, 10 mL) was hydrogenated by using 10% palladium-on-carbon (200 mg) at room temperature and atmospheric pressure. The mixture was filtered and concentrated, and the product was crystallised from light petroleum–diethyl ether to yield **4a** (115 mg, 96%), m.p. 190–194°, $[\alpha]_D^{20}$ −49° (*c* 1, chloroform).

*1D-1,2,3,4,5-Penta-O-benzoyl-*myo*-inositol* (**4b**). — This compound was prepared from **3b** as described for **4a** and in comparable yield. It had m.p. 191–194°, $[\alpha]_D^{22}$ +47° (*c* 1, chloroform).

Racemic **4**, similarly obtained from **3**, had m.p. 127–128°.

Anal. Calc. for $C_{41}H_{32}O_{11} \cdot H_2O$: C, 68.5; H, 4.77. Found: C, 68.8; H, 4.72.

*1L-1,2,3,4,5-Penta-O-benzoyl-6-O-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-*myo*-inositol* (**5a**). — A mixture of **4a** (105 mg, 0.15 mmol), 2,3,4-tri-*O*-benzyl-1-*O*-(*N*-methylacetimidyl)-β-L-fucopyranose[9] (135 mg, 0.3 mmol), powdered 4 Å molecular sieves (0.5 g), and toluene-*p*-sulfonic acid (25 mg, 0.15 mmol) in benzene (5 mL) was stirred under nitrogen at room temperature for 3 days. Triethylamine (0.5 mL) was added, and the mixture was diluted with chloroform, filtered, and concentrated. A solution of the residue in chloroform was washed with aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), filtered, and concentrated. Column chromatography (hexane–ethyl acetate, 3:1) of the residue on silica gel afforded **5a** (138 mg, 83%), $[\alpha]_D^{22}$ −62° (*c* 0.7, chloroform).

*1D-1,2,3,4,5-Penta-O-benzoyl-6-O-(2,3,4-tri-O-benzyl-α-L-fucopyranosyl)-*myo*-inositol* (**5b**). — This compound was prepared from **4b** as described for **5a** and in comparable yield. It had $[\alpha]_D^{22}$ −13° (*c* 0.5, chloroform).

*1D-4-O-α-L-Fucopyranosyl-*myo*-inositol* (**6a**). — Compound **5a** (100 mg) was treated with a catalytic amount of sodium methoxide in methanol (5 mL) at room temperature for 2 h. The solution was neutralised with Dowex 50 (H^+) resin, filtered, and concentrated. The product was purified by column chromatography (ethyl acetate–methanol–water, 80:15:5) on silica gel, and a solution in acetic acid (3 mL) was hydrogenated by using 10% palladium-on-carbon (100 mg) at room temperature and atmospheric pressure. The mixture was filtered, concentrated, and purified on a column of Biogel P-2 to yield **6a** (24 mg, 82%), m.p. 241–243° (dec.) (from methanol–2-propanol), $[\alpha]_D^{22}$ −110° (*c* 0.2, water).

Anal. Calc. for $C_{12}H_{22}O_{10} \cdot H_2O$: C, 41.9; H, 7.03. Found: C, 41.9; H, 7.07.

*1L-4-O-α-L-Fucopyranosyl-*myo*-inositol* (**6b**). — This compound was prepared from **5b** as described for **6a** and in comparable yield. It had $[\alpha]_D^{22}$ −99° (*c* 0.4, water).

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