Carbohydrate Research, 173 (1988) 205–216
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

SYNTHESIS OF SOME BENZYL AND METHYL ETHERS OF *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)

(Received February 24th, 1987; accepted for publication, August 13th, 1987)

ABSTRACT

The 1D and 1L forms of 1,2,4,5,6- and 1,2,3,4,5-penta-*O*-methyl-*myo*-inositol have been prepared from the corresponding chiral mono-*O*-benzyl derivatives. Convenient preparations are also described of achiral derivatives of 1-, 2-, 4-, and 5-*O*-benzyl-*myo*-inositol and of achiral 1,2,4,5,6- and 1,3,4,5,6-*myo*-inositol by selective benzylation through stannylidene derivatives and through reductive cleavage of benzylidene acetals.

INTRODUCTION

In structural studies of naturally occurring glycosides of *myo*-inositol by methylation analysis, it would be valuable to have access to the six different penta-*O*-methyl derivatives and their acetates. We have reported on the synthesis of the two *meso*-forms, 1,3,4,5,6- and 1,2,3,4,6-penta-*O*-methyl-*myo*-inositol, and the two racemic forms, 1,2,4,5,6- and 1,2,3,4,5-penta-*O*-methyl-*myo*-inositol[1]. The corresponding acetates were well separated in g.l.c. We now report on the synthesis of the 1D and 1L forms of the two latter derivatives and their acetates. The intermediates, 1D- and 1L-1-*O*-benzyl-*myo*-inositol, which have previously been prepared by another route[2,3], may be useful in the synthesis of other chiral *myo*-inositol derivatives.

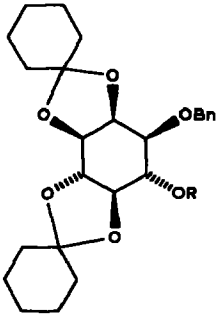
The preparation of other *O*-benzyl derivatives of *myo*-inositol by selective benzylation through stannylidene activation and through reductive cleavage of benzylidene acetals is also reported. Several of the substances described in this communication have been prepared by other routes, but the methods reported here are simpler and the yields for most of them are improved.

RESULTS AND DISCUSSION

Chiral derivatives. — The mono-isopropyl ester of 2,3-di-*O*-benzoyl-L-(+)-tartaric acid[4] was converted into the acid chloride which was used for acylation of

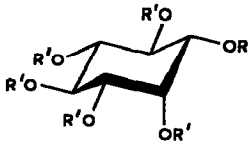
0008-6215/88/$ 03.50

racemic 1-*O*-benzyl-2,3:4,5-di-*O*-cyclohexylidene-*myo*-inositol (**1a** + **1b**)[1]. Chromatography then gave the diastereomers **2a** and **2b** (only one enantiomer is shown in the formulae). Saponification of **2a** and **2b**, followed by acid hydrolysis, yielded 1D- (**3a**) and 1L-1-*O*-benzyl-*myo*-inositol (**3b**). The overall yields were much higher than those obtained by a laborious route proceeding *via* D-mannose orthoester derivatives[2,3,5]. Acetylation of **3a** and **3b** yielded 1L- (**4a**) and 1D-1,2,4,5,6-penta-*O*-acetyl-3-*O*-benzyl-*myo*-inositol (**4b**). The monobenzyl ethers were then methylated, yielding 1D- (**5a**) and 1L-1-*O*-benzyl-2,3,4,5,6-penta-*O*-methyl-*myo*-inositol (**5b**), respectively, which were not isolated but hydrogenolysed to give 1L- (**6a**) and 1D-1,2,4,5,6-penta-*O*-methyl-*myo*-inositol (**6b**), characterised as the acetates **7a** and **7b**.

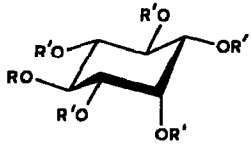


1a R = H

2a R = C=O
HCOBz
BzOCH
CO_2CHMe_2



3a R = Bn, R' = H
4a R = Bn, R' = Ac
5a R = Bn, R' = Me
6a R = H, R' = Me
7a R = Ac, R' = Me



8a R = Bn, R' = H
9a R = Bn, R' = Ac
10a R = Bn, R' = Me
11a R = H, R' = Me
12a R = Ac, R' = Me

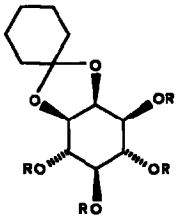
1D-4-*O*-Benzyl-*myo*-inositol (**8a**) and its enantiomer (**8b**)[6] were acetylated to give 1D- (**9a**) and 1L-1,2,3,5,6-penta-*O*-acetyl-4-*O*-benzyl-*myo*-inositol (**9b**). Methylation of **8a** and **8b** yielded 1D- (**10a**) and 1L-4-*O*-benzyl-1,2,3,5,6-penta-*O*-methyl-*myo*-inositol (**10b**), respectively, and hydrogenolysis then yielded 1L- (**11a**) and 1D-1,2,3,4,5-penta-*O*-methyl-*myo*-inositol (**11b**), which were characterised as the acetates **12a** and **12b**.

In methylation analysis of a monoglycosylated *myo*-inositol, one of the six possible penta-*O*-methyl-*myo*-inositols will be obtained. The two *meso*-forms and the two racemic forms, as their acetates, are well separated by g.l.c.[1]. The enantiomers **7a** and **7b** show $[\alpha]_D$ −7° and +7°, respectively, in chloroform, and the corresponding values for **12a** and **12b** are +1° and −1°, respectively. Methylation analysis is generally performed on a small scale, and it would be impractical to distinguish between these enantiomers by determining their optical rotations. C.d. is

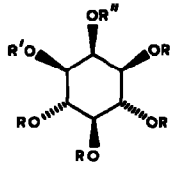
much more sensitive; thus, **7a** has λ_{max} 214 nm (θ +2284), **7b** has λ_{max} 214 nm (θ −2270), **12a** has λ_{max} 209 nm (θ +1039), and **12b** has λ_{max} 209 nm (θ −1035).

As a first approximation, the sign of the Cotton effect in the c.d. spectra of glycoside monoacetates[7] depends upon the dihedral angles between the AcO group and its vicinal oxygen atoms. When these are positive, a positive Cotton effect is observed. However, when they have different signs, it is difficult to estimate the sign of the Cotton effects. The values for **7a** and **7b** accord with this empirical rule, but the values for **12a** and **12b** can not be predicted.

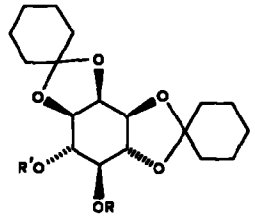
Selective benzylation through stannylidene activation[8,9]. — Starting from racemic 1,2-*O*-cyclohexylidene-*myo*-inositol[10,11] (**13**), the corresponding tetra-*O*-benzyl[12], tetra-*O*-*p*-methoxybenzyl and tetra-*O*-benzoyl derivatives (**14**, **15**, and **16**) were prepared (only one enantiomer is shown in the formulae). Removal of the cyclohexylidene group by treatment with acid yielded the corresponding 1,4,5,6-tetra-*O*-substituted *myo*-inositols (**17**–**19**) with hydroxyl groups at positions 2 and 3. These derivatives were benzylated, using benzyl bromide and activation with dibutyltin oxide. As expected, the equatorial position was preferentially benzylated,



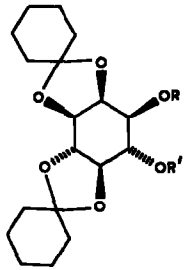
13 R = H
14 R = Bn
15 R = $CH_2C_6H_4OMe$
16 R = Bz



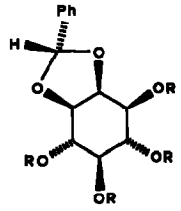
17 R = Bn, R′ = R″ = H
18 R = $CH_2C_6H_4OMe$, R′ = R″ = H
19 R = Bz, R′ = R″ = H
20 R = R′ = Bn, R″ = H
21 R = $CH_2C_6H_4OMe$, R′ = Bn, R″ = H
22 R = Bz, R′ = Bn, R″ = H
23 R = Bz, R′ = H, R″ = Bn
24 R = R″ = Bn, R′ = H



25 R = R′ = H
27 R = Bn, R′ = H
28 R = H, R′ = Bn



26 R = R′ = H
29 R = H, R′ = Bn



30a R = H
31a R = Bz
32a R = Bn

giving **20**–**23** as the main products.

When 1,2:3,4- (**25**) or 1,2:5,6-*O*-dicyclohexylidene-*myo*-inositol (**26**), each of which contains two vicinal equatorial hydroxyl groups, were subjected to the same treatment, no regioselectivity was observed, but the two monobenzyl ethers, (**27** + **28**) and (**1** + **29**), respectively, were formed in comparable yields.

Reductive cleavage of benzylidene acetals. — 1,2-*O*-Benzylidene-*myo*-inositol[13] (**30**) was prepared as a mixture of the *exo* (**30a**) and the *endo* (**30b**) isomers and converted into a mixture of the tetrabenzoates from which the *exo* (**31a**)[12] and *endo* (**31b**) derivatives were isolated. Benzylation similarly yielded a mixture of **32a** and **32b**. On treatment of **31** or **32** with sodium cyanoborohydride and hydrogen chloride in dichloromethane[13], the benzylidene group was reduced to a benzyl ether group and mixtures of isomers, (**22** + **23**) and (**20** + **24**), respectively, were obtained. However, the reaction is regiospecific, since the *exo* isomer (**31a**) yielded **22** and the *endo* isomer (**31b**) yielded **23**. Similar regioselectivity has been observed in other reductive ring-openings of benzylidene dioxolane rings[14].

EXPERIMENTAL

General methods. — These were the same as those previously reported[1]. ^{1}H- and ^{13}C-n.m.r. spectra were recorded at 25° and at 100 and 25 MHz, respectively. N.m.r. spectra for **1**–**12** are given in the text, and those for **13**–**32** in Tables I and II. C.d. spectra were recorded with a JASCO J41A spectropolarimeter.

1D-1-O-Benzyl-myo-*inositol* (**3a**). — A mixture of 2,3-di-*O*-benzoyl-L-(+)-tartaric anhydride (3.4 g), 2-propanol (6 mL), and chloroform (2 mL) was stirred for 3 h at 60°. The resulting clear solution was concentrated and toluene was distilled thrice from the residue to give isopropyl hydrogen 2,3-di-*O*-benzoyl-L-(+)-tartrate[4] as a syrup (4.0 g, 100%), $[\alpha]_D$ −88° (*c* 1.2, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 1.05 and 1.22 (2 d, each 3 H, *J* 6.5 Hz, CMe_2), 5.04 (septet, 1 H, *J* 6.5 Hz, $CHMe_2$), 5.91 and 6.04 (2 d, each 1 H, *J* 2.6 Hz, H-2,3).

A solution of the foregoing product (1.60 g) in thionyl chloride (15 mL) was heated for 1 h at 50°. The reaction was monitored by ^{1}H-n.m.r. spectroscopy. Higher temperatures and longer reaction times generated the anhydride. The solution was concentrated and toluene was distilled from the residue to give the acid chloride (1.67 g, 100%). ^{1}H-n.m.r. data ($CDCl_3$): δ 1.07 and 1.25 (2 d, each 3 H, *J* 6.2 Hz, CMe_2), 5.09 (septet, 1 H, *J* 6.2 Hz, $CHMe_2$), 6.16 (s, 2 H, H-2,3). The chloride was used immediately since the anhydride was generated on storage.

A solution of the foregoing acid chloride (1.67 g, 4.0 mmol) in dichloromethane (5 mL) was added at −55° to a stirred solution of (±)-1-*O*-benzyl-2,3:4,5-di-*O*-cyclohexylidene-*myo*-inositol[1] (**1**; 0.62 g, 1.44 mmol) in pyridine (1 mL) and dichloromethane (5 mL). T.l.c. (toluene–ethyl acetate, 4:1) showed that the reaction was complete after 20 min. The mixture was diluted with chloroform (30 mL), washed with saturated aqueous sodium hydrogencarbonate and saturated aqueous sodium chloride, dried ($MgSO_4$), filtered, and concentrated. Column chromato-

TABLE I

^{1}H-N.M.R. SPECTRA OF *myo*-INOSITOL DERIVATIVES[a,b]

	Chemical shifts (J in Hz) myo-*Inositol hydrogens*						
Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	
13	4.04 (4.9)	4.46 (3.8)	3.85 (9.5)	3.63 (8.9)	3.24 (10.0)	3.57 (7.6)	
14	3.68 (3.6)	4.27 (5.5)	4.09 (6.8)	3.81 (9.4)	3.40 (8.3)	3.94 (8.4)	
15[c]	3.62 (3.7)	4.22 (5.4)	4.04 (6.7)	3.75 (9.5)	3.33 (8.3)	3.88 (8.3)	
16	5.75 (4.0)	4.85 (5.5)	4.58 (6.5)	5.92 (9.0)	5.71 (8.7)	6.23 (9.6)	
17	3.46† (2.8)	4.20 (2.8)	3.43† (9.4)	3.84* (9.4)	3.47 (9.4)	3.94* (9.4)	
18	3.39 (2.6)	4.13 (2.6)	3.39 (9.9)	3.79* (9.9)	3.40 (9.9)	3.91* (9.9)	
19	5.46 (2.7)	4.62 (2.7)	4.12 (10.0)	5.75 (—) —	6.09 (10.0)	6.36 (10.0)	
20	3.37 (2.4)	4.21 (2.4)	3.37 (9.3)	4.01 (9.3)	3.44 (9.3)	4.01 (9.3)	
21	3.37 (2.6)	4.17 (2.6)	3.37 (9.4)	3.93* (9.4)	3.39 (9.4)	3.96* (9.4)	
22	5.38 (2.7)	4.68 (2.6)	3.91 (9.5)	6.12 (9.9)	5.77 (9.9)	6.33 (10.0)	
23	5.45 (2.4)	4.43 (2.8)	4.09 (—)	5.75 (—) —	5.99 (—)	6.32 (10.5)	
24	3.48* (2.4)	4.02 (2.4)	3.45* (9.3)	4.06† (9.3)	3.47 (9.3)	3.82† (9.3)	
25	4.21 (5.4)	4.62 (2.7)	3.60—3.83 (—)	3.99 (—)	3.60 (—) —	3.83 (—)	
26	4.31 (6.1)	4.49 (4.1)	3.81 (5.0)	4.03 (8.8)	3.39 (10.0)	3.91 (8.9)	
27	4.20 (5.5)	4.60 (3.1)	3.70 (9.8)	4.07 (9.0)	3.52 (6.5)	3.87 (5.5)	
28	4.38 (6.1)	4.62 (3.0)	3.73 (9.6)	4.02 (8.3)	3.85 (5.1)	3.66 (4.4)	
1	3.56 (4.1)	4.39 (5.4)	4.20 (8.2)	3.78 (10.0)	3.30 (9.3)	4.09 (6.8)	
29	4.30 (—)	4.41 (3.2)	4.04 (2.1)	3.91 (7.8)	3.55 (10.0)	4.12 (—)	
31a	5.80 (—)	4.82 (—) —	4.89 (—)	6.11 (9.7)	5.79 (8.3)	6.24 (9.4)	*acetal-H* 6.50
31b	5.88 (3.8)	4.97 (6.3)	4.76 (6.0)	5.98 (8.4)	5.78 (7.6)	6.23 (9.4)	5.97
32a	3.7–4.1 (—)	4.35 (—) —	4.43 (—)	3.7–4.1 (—)	3.51 (—)	3.7–4.1 (—)	6.13
32b	3.84 (6.5)	4.43 (3.3)	4.28 (6.1)	3.98 (9.8)	3.54 (6.7)	3.99 (7.3)	5.88

[a]Chemical shifts (δ in p.p.m.) for solutions in $CDCl_3$ with Me_4Si as internal standard, except for compound 1 which was measured in D_2O with acetone (δ 2.225) as internal standard. [b] *, †, Indicates shift assignment may be exchanged. [c]Compound 15 is assigned as 2,3-*O*-cyclohexylidene-

TABLE II

^{13}C-N.M.R. CHEMICAL SHIFT DATA FOR *myo*-INOSITOL DERIVATIVES[a,b]

	myo-*Inositol carbons*						*Other carbons*	
Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*Acetal-C,*	*-CH_2- and C=O*
13	78.8	76.5	70.4	73.0	73.4	75.9	112.0	
14	77.1	73.8	78.6	82.7	81.9	80.7	110.2	72.9, 73.8, 75.0, 75.1
15[c]	76.8	73.9	78.7	82.6	81.7	80.5	110.1	72.6, 73.6, 74.7, 74.8 *p*-MeO: 55.1
16	69.9	73.1	75.6	73.1	71.3	69.9	111.8	164.9, 165.0, 165.2 165.4
17	79.8	69.0	71.5	81.1*	83.0	81.4*		72.5, 75.4, 75.5, 75.8
18	79.5	69.0	71.5	80.8*	82.8	81.2*		72.1, 75.0, 75.1, 75.4 *p*-MeO: 55.1
19	72.1	70.4	71.0	73.6	70.7	69.8		164.8, 165.0, 165.3
20	79.6	67.3	79.6	81.0	83.0	81.0		72.6, 75.8
21	79.7*	67.3	79.4*	80.8	82.8	80.8		72.1, 72.5, 75.3 *p*-MeO: 55.1
22	71.9	67.2	76.7	71.2	71.0	69.7		72.1, 165.1, 165.2 165.4, 165.6
23	72.6	77.7	71.1	73.7	70.8	70.1		75.8, 165.3, 165.4
24	80.7	76.9	72.2	81.9*	83.4	81.7*		72.8, 74.6, 75.4, 75.7
25	80.6	71.8	74.9*	74.7	74.2*	78.6	112.5	
26	76.1	75.4	74.3	73.1	77.9	77.7	110.9, 112.9	
27	80.1	71.5	75.0	75.0	81.4	76.7	112.1	72.1
28	79.4	72.6	74.4	75.3	73.9	84.7	111.9, 112.2	72.6
1	80.5	74.0	75.7	78.2	77.3	71.8	110.7, 112.4	72.6
29	76.5	75.1	72.1	79.7	78.7	76.5	111.1, 112.7	71.5
31a	70.0	73.6	77.3	70.9*	70.8*	70.0	104.0	165.0, 165.2, 165.3
31b	69.6	75.1	76.0	73.1	72.1	70.2	105.1	164.6, 164.9, 165.2
32a	77.3	74.8	79.6*	80.4*	81.8	79.9*	103.2	72.9, 73.7, 74.2, 74.4
32b	76.3	75.0	78.9	81.7*	82.1	80.6*	104.2	72.9, 73.3, 74.1, 74.5

[a]Chemical shifts (δ in p.p.m.) for solutions in $CDCl_3$ with Me_4Si as internal standard, except for compound **1** which was measured in D_2O with 1,4-dioxane (δ 67.40) as internal standard. N.m.r. assignments were based upon selective decouplings and off-resonance experiments. [b] *, Indicates that shift assignment may be exchanged. [c]Compound **15** is assigned as 2,3-*O*-cyclohexylidene-1,4,5,6-tetra-*O*-*p*-methoxybenzyl-*myo*-inositol.

graphy (silica gel; chloroform–ethyl acetate, 50:1) gave 90% of the material as the pure diastereomers, and the remaining mixed fraction was subjected once to further chromatography. 1D-1-*O*-Benzyl-2,3:4,5-di-*O*-cyclohexylidene-*myo*-inositol 6-(isopropyl 2,3-di-*O*-benzoyl-L-(+)-tartrate) (**2a**; 530 mg, 45%) had $[\alpha]_D$ −39° (*c* 1.1, chloroform), R_F 0.68. N.m.r. data ($CDCl_3$): ^{1}H, δ 1.07 and 1.26 (2 d, each 3 H, CMe_2), 1.18–1.73 (m, 20 H, 10 CH_2), 3.35 (dd, 1 H, H-1), 3.61 (dd, 1 H, H-5), 4.01 (dd, 1 H, H-2), 4.13–4.35 (m, H-3,4, AB spectrum), 4.33 and 4.58 (2 d, 2 H, CH_2Ph), 5.08 (septet, 1 H, $CHMe_2$), 5.21 (dd, 1 H, H-6), 6.09 and 6.18 [(2 d, 2 H, -CH(OBz)CH(OBz)-], 7.19 (s, 5 H, $PhCH_2$), 7.30–7.72 and 8.04–8.22 (m, 10 H, 2 PhCO), $J_{1,2}$ 3.7, $J_{2,3}$ 6.8, $J_{4,5}$ 10.2, $J_{5,6}$ 7.8, $J_{1,6}$ 1.2, J_{CH,CH_3} 6.3, J_{CH_2Ph} 11.9, $J_{CH(OBz),CH(OBz)}$ 2.9 Hz; ^{13}C, δ 21.4 and 21.15 [$C(CH_3)_2$], 23.4, 24.7, 24.9, 34.3,

35.4, 36.2, and 36.4 (10 CH_2), 70.3 [-*C*H(CH_3)$_2$], 71.0 and 71.1 [-CH(OBz) CH(OBz)-], 72.8 (*C*H_2Ph), 73.8 (C-2), 75.4 (C-5), 75.8 and 2 × 76.0 (C-3,4,6), 79.0 (C-1), 111.6 and 113.2 (acetal C), 127.0–137.3 (12 C, aromatic), 164.4, 164.6, 164.9 (C=O).

1L-1-*O*-Benzyl-2,3:4,5-di-*O*-cyclohexylidene-*myo*-inositol 6-(isopropyl 2,3-di-*O*-benzoyl-L-(+)-tartrate) (**2b**; 535 mg, 46%) had $[\alpha]_D$ −39° (*c* 1.1, chloroform), R_F 0.59. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.09 and 1.25 (2 d, each 3 H, CMe_2), 1.05–1.61 (m, 20 H, 10 CH_2), 3.40 (dd, 1 H, H-5), 3.68 (dd, 1 H, H-1), 4.03 (dd, 1 H, H-4), 4.18–4.40 (m, 2 H, H-2,3, AB spectrum), 4.71 (s, 2 H, C*H*$_2$Ph), 5.08 (septet, 1 H, C*H*Me_2), 5.33 (dd, 1 H, H-6), 5.92 and 6.05 [2 d, each 1 H, -*CH*(OBz)*CH*(OBz)-], 7.30 (s, 5 H, *Ph*CH_2), 7.30–7.70 and 7.95–8.18 (m, 10 H, 2 PhCO), $J_{1,2}$ 3.7, $J_{3,4}$ 6.8, $J_{4,5}$ 10.2, $J_{5,6}$ 8.5, $J_{1,6}$ 3.4, J_{CH,CH_3} 6.4, $J_{CH(OBz),CH(OBz)}$ 2.7 Hz; ^{13}C, δ 21.4 and 21.6 [C(*C*H_2)$_3$], 23.2, 23.6, 23.8, 24.7, 25.0, 34.6, 35.8, 35.9, and 36.3 (10 CH_2), 70.2 [-*C*H(CH_2)$_3$], 71.0 and 71.3 [-*C*H(OBz)*C*H(OBz)-], 72.3 (*C*H_2Ph), 74.1 (C-2), 75.1 (C-6), 75.3 (C-5), 76.0 (C-3), 76.7 (C-4), 77.9 (C-1), 111.6 and 113.0 (acetal C), 127–137.1 (12 C, aromatic), 164.4, 164.7, and 164.8 (C=O).

Compound **2a** (470 mg, 0.59 mmol) was treated with methanolic 0.15M sodium methoxide (10 mL) for 2 h at room temperature. The solution was neutralised with Dowex 50 (H^+) resin, filtered, and concentrated. The product was treated with aqueous 90% trifluoroacetic acid (10 mL) for 15 min at room temperature and concentrated, and toluene was distilled from the residue. Recrystallisation from ethanol–2-propanol then yielded **3a** (130 mg, 82%), m.p. 210–211°, $[\alpha]_D$ −26° (*c* 0.7, methanol); lit.[3] m.p. 210–211°, $[\alpha]_D$ −33° (methanol). ^{1}H-N.m.r. data (internal acetone at 2.225 p.p.m., D_2O): δ 3.26 (dd, 1 H, H-5), 3.39 (dd, 1 H, H-1), 3.44 (dd, 1 H, H-3), 3.67 (dd, 1 H, H-4), 3.75 (dd, 1 H, H-6), 4.25 (dd, 1 H, H-2), 4.64 and 4.73 (2 d, 2 H, C*H*$_2$Ph), 7.45 (s, 5 H, aromatic H), $J_{1,2} = J_{1,3} = 2.6$, $J_{4,5} = J_{1,6} = 9.8$, $J_{4,5} = J_{5,6} = 9.0$ Hz; ^{13}C (internal 1,4-dioxane at 67.40 p.p.m., D_2O); δ 69.5 (C-2), 71.9 (C-3), 72.4 (*C*H_2Ph), 72.6 (C-6), 73.1 (C-4), 75.1 (C-5), 79.4 (C-1), 129.0, 129.3, 129.4, and 138.1 (aromatic C).

Anal. Calc. for $C_{13}H_{18}O_6$: C, 57.8; H, 6.7. Found: C, 57.5; H, 6.7.

The penta-acetate (**4a**) of **3a** had m.p. 187–188°, $[\alpha]_D$ −39° (*c* 0.8, chloroform); lit.[5] m.p. 180–182°, $[\alpha]_D$ −26.5° (chloroform).

1L-1-O-Benzyl-myo-*inositol* (**3b**). — Prepared from **2b**, as described above for **3a**, **3b** had m.p. 210–211°, $[\alpha]_D$ +25° (*c* 0.5, methanol); lit.[2,3] m.p. 210–211°, $[\alpha]_D$ +33° (methanol).

The penta-acetate (**4b**) of **3b** had m.p. 186–188°, $[\alpha]_D$ +39° (*c* 1, chloroform); lit.[8] m.p. 181–183°, $[\alpha]_D$ +29° (chloroform).

1L-1,2,4,5,6-Penta-O-methyl-myo-*inositol* (**6a**). — Compound **3a** (115 mg, 0.426 mmol) was methylated with iodomethane (2 mL) and sodium methylsulfinylmethanide (prepared from 0.3 g of sodium hydride) in methyl sulfoxide (3 mL) for 1 h. Methanol (2 mL) was added, and the solution was concentrated to 2 mL and transferred using toluene to the top of a column of silica gel. Elution with toluene–acetone (1:1) yielded a product which was hydrogenolysed in ethanol (3 mL) over

10% Pd/C (200 mg) for 45 h at room temperature and atmospheric pressure. The mixture was filtered through Celite and concentrated. Column chromatography (toluene–acetone, 1:2) of the residue gave **6a** (76 mg, 72%) which, after recrystallisation from light petroleum–ether, had m.p. 116–118°, $[\alpha]_D$ −4° (*c* 0.8, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 2.48 (s, 1 H, OH), 2.86–3.07 (m, 2 H, H-3,5), 3.20–3.64 (m, 18 H, 5 × CH_3, H-1,4,6), 3.79 (t, 1 H, H-2), $J_{1,2} = J_{2,3} = 2.4$ Hz; ^{13}C, δ 58.4, 60.6, 60.9, and 61.2 (5 OCH_3), 71.9 (C-1), 77.7 (C-2), 82.6 (C-3), 82.9, 83.1 (C-4,6), 85.3 (C-5). The n.m.r. assignments were based on those for 1-*O*-benzyl-2,3,4,5,6-penta-*O*-methyl-*myo*-inositol and upon selective decouplings.

Anal. Calc. for $C_{11}H_{22}O_6$: C, 52.8; H, 8.9. Found: C, 52.9; H, 8.9.

1D-1,2,4,5,6-Penta-O-*methyl*-myo-*inositol* (**6b**). — Compound **3b** (90 mg) was methylated and the product was hydrogenolysed as described for **3a**, to yield **6b** (70 mg, 84%), m.p. 116–118°, $[\alpha]_D$ +4° (*c* 0.9, chloroform).

Anal. Calc. for $C_{11}H_{22}O_6$: C, 52.8; H, 8.9. Found: C, 52.8; H, 8.9.

1D-1-O-*Acetyl-2,3,4,5,6-penta*-O-*methyl*-myo-*inositol* (**7a**). — Conventional acetylation of **6a** (60 mg) and column chromatography (toluene–acetone, 3:1) of the product yielded **7a** (66 mg, 94%), $[\alpha]_D$ −7° (*c* 0.8, chloroform). N.m.r. ($CDCl_3$): ^1H, δ 2.15 (s, 3 H, Ac), 2.99 (dd, 1 H, H-5), 3.06 (dd, 1 H, H-3), 3.44 (dd, 1 H, H-4), 3.48, 3.55, 3.61, and 3.62 (4 s, 15 H, 5 OMe), 3.45–3.64 (m, 1 H, H-6), 3.79 (dd, 1 H, H-2), 4.63 (dd, 1 H, H-1), $J_{1,2} = J_{1,3} = 2.4$, $J_{3,4}$ 9.8, $J_{4,5} = J_{5,6} = 9.0$, $J_{1,6}$ 10.2 Hz; ^{13}C, δ 21.1 (CH_3CO), 58.5, 60.8, 60.9, and 61.1 (OCH_3), 73.8 (C-1), 76.7 (C-2), 80.6 (C-6), 81.8 (C-3), 82.6 (C-4), 85.1 (C-5), 170.1 (C=O). The n.m.r. assignments were based upon selective decouplings.

Anal. Calc. for $C_{13}H_{24}O_7$: C, 53.4; H, 8.3. Found: C, 53.0; H, 8.8.

1L-1-O-*Acetyl-2,3,4,5,6-penta*-O-*methyl*-myo-*inositol* (**7b**). — Conventional acetylation of **6b** gave **7b**, $[\alpha]_D$ +7° (*c* 0.8, chloroform).

Anal. Calc. for $C_{13}H_{24}O_7$: C, 53.4; H, 8.3. Found: C, 52.9; H, 7.8.

1D-1,2,3,5,6-Penta-O-*acetyl-4*-O-*benzyl*-myo-*inositol* (**9a**). — Conventional acetylation of **8a**[5] gave **9a**, m.p. 131–132°, $[\alpha]_D$ −26° (*c* 1, chloroform).

Anal. Calc. for $C_{23}H_{28}O_{11}$: C, 57.5; H, 5.9. Found: C, 57.5; H, 5.9.

1L-1,2,3,5,6-Penta-O-*acetyl-4*-O-*benzyl*-myo-*inositol* (**9b**). — Conventional acetylation of **8b**[5] gave **9b**, m.p. 131–132°, $[\alpha]_D$ +26° (*c* 0.4, chloroform).

Anal. Calc. for $C_{23}H_{28}O_{11}$: C, 57.5; H, 5.9. Found: C, 57.0; H, 5.7.

1L-1,2,3,4,5-Penta-O-*methyl*-myo-*inositol* (**11a**). — Compound **8a** (180 mg) was methylated and the product was hydrogenolysed as described for **3a**, to yield **11a** (134 mg, 80%), $[\alpha]_D$ +5° (*c* 0.8, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 2.68 (s, 1 H, OH), 2.94 (dd, 1 H, H-1 or H-3), 2.96 (dd, 1 H, H-5), 3.01 (dd, 1 H, H-3 or H-1), 3.48 (dd, 1 H, H-6), 3.51, 3.52, 3.60, 3.61, 3.64 (5 s, 15 H, 5 OMe), 3.85 (dd, 1 H, H-4), 3.92 (dd, 1 H, H-2), $J_{1,2} = J_{2,3} = 2.4$, $J_{3,4} = J_{1,6} = 9.7$, $J_{4,5} = J_{5,6} = 9.1$ Hz; ^{13}C, δ 57.8, 58.4, 60.5, 60.7, and 60.8 (5 OCH_3), 71.7 (C-4), 74.2 (C-2), 82.0, 82.5, and 82.6 (C-1,3,6), 84.5 (C-5). The n.m.r. assignments were based upon selective decouplings.

Anal. Calc. for $C_{11}H_{22}O_6$: C, 52.8; H, 8.9. Found: C, 52.4; H, 9.0.

1D-1,2,3,4,5-Penta-O-methyl-myo-inositol (**11b**). — Compound **8b** (159 mg) was methylated and the product was hydrogenolysed as described for **3a**, to yield **11b** (100 mg, 68%), $[\alpha]_D$ −5° (*c* 1, chloroform).

Anal. Calc. for $C_{11}H_{22}O_6$: C, 52.8; H, 8.9. Found: C, 52.8; H, 9.2.

1D-4-O-Acetyl-1,2,3,5,6-penta-O-methyl-myo-inositol (**12a**). — Conventional acetylation of **11a** (122 mg) yielded **12a** (135 mg, 95%), m.p. 112–114° (from light petroleum), $[\alpha]_D$ +1° (*c* 0.9, chloroform). N.m.r. data ($CDCl_3$): ^1H, δ 2.10 (s, 3 H, Ac), 2.99 (dd, 1 H, H-1), 3.05 (dd, 1 H, H-3), 3.06 (dd, 1 H, H-5), 3.41, 3.49, 3.51, 3.59, and 3.61 (5 s, 15 H, 5 OMe), 3.56 (dd, 1 H, H-6), 3.90 (dd, 1 H, H-2), 5.31 (dd, 1 H, H-4), $J_{1,2} = J_{2,3} = 2.4$, $J_{3,4}$ 10.2, $J_{4,5} = J_{1,6} = 9.5$, $J_{5,6}$ 9.8 Hz; ^{13}C, δ 21.1 CH_3CO), 58.1, 58.4, 60.0, 60.8, and 60.9 (5 OCH_3), 72.7 (C-4), 74.6 (C-2), 80.5 (C-3), 82.0 (C-1), 82.3 (C-6), 82.8 (C-5), 169.6 (C=O).

Anal. Calc. for $C_{13}H_{24}O_7$: C, 53.4; H, 8.3. Found: C, 53.4; H, 8.6.

1L-4-O-Acetyl-1,2,3,5,6-penta-O-methyl-myo-inositol (**12b**). — Conventional acetylation of **11b** gave **12b**, m.p. 112–114°, $[\alpha]_D$ −1° (*c* 1.1, chloroform).

Anal. Calc. for $C_{13}H_{24}O_7$: C, 53.4; H, 8.3. Found: C, 53.3; H, 8.5.

Selective monobenzylation involving activation by dibutyltin oxide. — A suspension of the *myo*-inositol derivative (1.0 mol) and dibutyltin oxide (1.05 mmol) in toluene (25 mL) was boiled under reflux with azeotropic removal of water for 3 h, and then concentrated to 10 mL. Benzyl bromide (2.0 mmol) and tetrabutylammonium bromide (0.5 mmol) were added, the solution was stirred at 70° until the reaction was complete (t.l.c.) and then concentrated, and the product(s) were isolated by chromatography on silica gel.

(±)-*1,2-O-Cyclohexylidene-myo-inositol* (**13**). — A mixture of *myo*-inositol (1.8 g, 10 mmol), 1-ethoxycyclohexene (2.5 g, 20 mmol), and toluene-*p*-sulfonic acid monohydrate (100 mg) in *N,N*-dimethylformamide (20 mL) was stirred for 1 h at 100–110°. The clear solution was cooled and concentrated. Toluene (20 mL), hexane (10 mL), ether (20 mL), ethanol (5 mL), and trifluoroacetic acid (2 mL) were added and the solution was stored at ~5°. The crude product (2.84 g, 90%) was recrystallised from ethanol–ether to give **13** (2.05 g, 79%), m.p. 176–178°; lit.[13] m.p. 181–183°.

1,4,5,6-Tetra-O-p-methoxybenzyl-myo-inositol (**18**). — A solution of *p*-methoxybenzyl bromide (17.7 g, 88 mmol) in *N,N*-dimethylformamide (15 mL) was added dropwise to a stirred solution of **13** (3.0 g, 11.5 mmol) and sodium hydride (1.68 g, 70 mmol) in *N,N*-dimethylformamide (35 mL) at 0°. The mixture was allowed to attain room temperature. After 16 h, excess of hydride was decomposed with methanol, and the solution was diluted with chloroform, washed three times with water, and concentrated. Flash column chromatography (toluene→toluene–ethyl acetate, 6:1) of the residue gave syrupy **15** (4.93 g, 57%).

A solution of **15** (1.30 g) in ethanol (15 mL), chloroform (3 mL), and M hydrochloric acid (3 mL) was heated for 3 h at 60°, then neutralised, and worked-up as described for **19**. The product crystallised from ether–dichloromethane–light petroleum to yield **18** (865 mg, 74%), m.p. 116–117°. Recrystallisation gave material

(760 mg, 65%) with m.p. 123–124°.

Anal. Calc. for $C_{38}H_{44}O_{10}$: C, 69.1; H, 6.7. Found: C, 69.0; H, 6.6.

*1,4,5,6-Tetra-O-benzoyl-*myo*-inositol* (**19**). — A solution of 1,4,5,6-tetra-*O*-benzoyl-2,3-*O*-cyclohexylidene-*myo*-inositol[15] (**16**, 2.0 g) in acetic acid (40 mL), ethanol (10 mL), and M sulfuric acid (10 mL) was heated for 4 h at 80°, then cooled, neutralised with M sodium hydroxide, and extracted with chloroform. The extract was washed with aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), filtered, and concentrated. Column chromatography (chloroform–ethyl acetate, 6:1) of the residue gave **19** (1.44 g, 82%) which, after recrystallisation from ether–light petroleum, had m.p. 216–217°.

Anal. Calc. for $C_{34}H_{28}O_{10}$: C, 68.5; H, 4.7. Found: C, 68.2; H, 4.8.

*1,3,4,5,6-Penta-O-benzyl-*myo*-inositol* (**20**). — 1,4,5,6-Tetra-*O*-benzyl-*myo*-inositol[12] (**17**, 650 mg) was subjected to stannylidene-activated benzylation. Column chromatography (toluene–ethyl acetate, 4:1) of the product and crystallisation from ether–light petroleum gave **20** (620 mg, 82%), m.p. 127–128°; lit.[9] m.p. 128–130°.

*1-O-Benzyl-3,4,5,6-tetra-O-p-methoxybenzyl-*myo*-inositol* (**21**). — Compound **18** (661 mg) was subjected to stannylidene-activated benzylation. Column chromatography (toluene–ethyl acetate, 2:1) of the product and crystallisation from ether–light petroleum gave **21** (0.91 g, 80%), m.p. 138–140°.

Anal. Calc. for $C_{45}H_{50}O_{10}$: C, 72.0; H, 6.7. Found: C, 72.0; H, 6.6.

*1,4,5,6-Tetra-O-benzoyl-3-O-benzyl-*myo*-inositol* (**22**). — Compound **19** (596 mg) was subjected to stannylidene-activated benzylation. Short-column chromatography (toluene–ethyl acetate, 2:1) followed by column chromatography (chloroform–ethyl acetate, 10:1) of the product yielded, first, two minor products, namely, 1,4,5,6-tetra-*O*-benzoyl-2-*O*-benzyl-*myo*-inositol (**23**; 20 mg, 3%) and 1,2,4,5-tetra-*O*-benzoyl-3-*O*-benzyl-*myo*-inositol (65 mg, 10%, identified from the ^1H- and ^{13}C-n.m.r. data). Further elution gave **22** (410 mg, 60%), m.p. 212–215°. Eluted last were two minor products (combined yield, 10%) that were identified tentatively by ^1H-n.m.r. spectroscopy as 2,4,5,6-tetra-*O*-benzoyl-1-*O*-benzyl- and 4,5,6-tri-*O*-benzoyl-1,3-di-*O*-benzyl-*myo*-inositol.

*5- (**27**) and 6-O-Benzyl-1,2:3,4-di-O-cyclohexylidene-*myo*-inositol* (**28**). — 1,2:3,4-Di-*O*-cyclohexylidene-*myo*-inositol (**25**, 680 mg) was subjected to stannylidene-activated benzylation for 3 days. Short-column chromatography (toluene–ethyl acetate, 2:1) of the product, followed by column chromatography, gave, first, **28** (0.335 g, 39%), m.p. 124–126° (lit.[1] m.p. 125–126°), and then **27** (0.43 g, 50%) as a syrup.

*1-O-Benzyl-2,3:4,5-di-O-cyclohexylidene-*myo*-inositol* (**1**) *and 4-O-benzyl-1,2:5,6-di-O-cyclohexylidene-*myo*-inositol* (**29**). — 1,2:5,6-Di-*O*-cyclohexylidene-*myo*-inositol (**26**, 680 mg) was subjected to stannylidene benzylation for 2 days. Column chromatography (toluene–ethyl acetate, 4:1) of the product, as described for **27** and **28**, gave, first, **29** (0.37 g, 43%) and then **1** (0.40 g, 46%) as syrups[1].

*1,4,5,6-Tetra-O-benzoyl-2,3-O-benzylidene-*myo*-inositol* (**31ab**). — α,α-Dimethoxytoluene (1.2 mL, 8 mmol) in *N,N*-dimethylformamide (3 mL) was added

with stirring to a solution of *myo*-inositol (0.90 g, 5 mmol) and toluene-*p*-sulfonic acid (50 mg) in *N,N*-dimethylformamide (10 mL) at 100°. After 1 h, the solution was neutralised with sodium carbonate and concentrated. Flash column chromatography (dichloromethane → chloroform–methanol, 2:1) of the syrupy residue gave 1,2-*O*-benzylidene-*myo*-inositol[13] (**30**; 0.92 g, 68%) containing (n.m.r. data) equal amounts of the *exo* and *endo* isomers.

Compound **30** (0.88 g) was treated conventionally with benzoyl chloride (3.0 mL) in pyridine (20 mL) overnight at room temperature. Recrystallisation of the product from dichloromethane–light petroleum gave the *exo* and *endo* isomers as a crystalline mixture (1.93 g, 86%). Fractional crystallisation of the mixture from light petroleum–ether gave the *exo* isomer **31a**, m.p. 272–274° [lit.[13] m.p. 280° (dec.)], R_F 0.88 (toluene–ethyl acetate, 9:1).

Fractional crystallisation of the mixture from dichloromethane–methanol gave **31b**, m.p. 221–223°, R_F 0.84.

Anal. Calc. for $C_{41}H_{32}O_{10}$: C, 71.9; H, 4.7. Found: C, 71.8; H, 4.6.

1,4,5,6-Tetra-O-*benzyl-2,3*-O-*benzylidene*-myo-*inositols* (**32ab**). — A solution of **30** (0.94 g) in *N,N*-dimethylformamide (25 mL) was treated with sodium hydride (600 mg) and benzyl bromide (2.7 mL) for 3 h at room temperature. Excess of benzyl bromide was destroyed with methanol (5 mL), and the mixture was diluted with toluene (100 mL), washed with water, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (toluene–ethyl acetate, 20:1) of the product gave a mixture (1.79 g, 81%) of the *exo* (**32a**) and *endo* (**32b**) isomers. Column chromatography then gave the pure isomers (see Tables I and II for the n.m.r. data).

Reductive acetal cleavage of 1,4,5,6-tetra-O-*benzoyl-2,3*-O-*benzylidene*-myo-*inositol* (**31**). — Saturated ethereal hydrogen chloride was added dropwise to a solution of sodium cyanoborohydride (430 mg, 8 mmol) in dry dichloromethane (10 mL) until the evolution of hydrogen decreased and then another 5 mL were added, followed by a solution of the mixture (684 mg, 1.00 mmol) of **31a** and **31b** in CH_2Cl_2 (10 mL). T.l.c. (toluene–ethyl acetate, 6:1) indicated that the reaction was completed almost immediately. The mixture was diluted with dichloromethane, washed with saturated aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), filtered, and concentrated, and the residue was subjected to column chromatography (chloroform–ethyl acetate, 10:1). Small-scale experiments, starting with the pure isomers **31a** and **31b**, showed that **22** was formed from the *exo* isomer **21a**, and **23** from **21b**.

1,4,5,6-Tetra-*O*-benzoyl-3-*O*-benzyl-*myo*-inositol (**22**; 320 mg, 46%) had m.p. 212–215° (from ether–pentane), R_F 0.55.

Anal. Calc. for $C_{41}H_{34}O_{10}$: C, 71.7; H, 5.0. Found: C, 71.7; H, 5.0.

1,4,5,6-Tetra-*O*-benzoyl-2-*O*-benzyl-*myo*-inositol (**23**; 290 mg, 42%) had m.p. 205–207° (from ether–pentane), R_F 0.69.

Anal. Calc. for $C_{41}H_{34}O_{10}$: C, 71.7; H, 5.0. Found: C, 71.8; H, 5.0.

Reductive acetal cleavage of 1,4,5,6-tetra-O-*benzyl-2,3*-O-*benzylidene*-myo-*inositol* (**32**). — The *endo/exo* mixture (0.8 g) **32ab** was treated with sodium

cyanoborohydride and hydrogen chloride as described for the preparation of **22** and **23**. Column chromatography (chloroform–ethyl acetate, 50:1) of the product afforded a crystalline mixture (0.64 g, 80%) of **20** and **24**. Selective crystallisation from ether gave 1,3,4,5,6-penta-*O*-benzyl-*myo*-inositol (**20**; 0.30 g, 38%), m.p. 126–127°; lit.[9] m.p. 128–130°. The mother liquor contained almost pure **24** which was recrystallised from light petroleum to yield 1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol (**24**; 0.26 g, 33%), m.p. 91–92°; lit.[12] m.p. 94–95°.

ACKNOWLEDGMENTS

The authors thank the Swedish Natural Science Research Council and the National Swedish Board for Technical Development for financial support, and Mr. Jan Glans (University of Lund) for recording the c.d. spectra.

REFERENCES

1 P. J. GAREGG, T. IVERSEN, R. JOHANSSON, AND B. LINDBERG, *Carbohydr. Res.*, 130 (1984) 322–326.
2 B. A. KLYASHCHITSKII, E. B. KRYLOVA, AND V. I. SHVETS, *Zh. Obshch. Khim.*, 42 (1972) 2586–2587; *Chem. Abstr.*, 78 (1973) 84692y.
3 A. P. KAPLUN, V. N. KRYLOVA, G. YU. SOLWEICHIK, B. A. KLYASHCHITSKII, AND V. I. SHVETS, *Zh. Org. Khim.*, 14 (1978) 1863–1867; *Chem. Abstr.*, 90 (1979) 23456a.
4 H. S. LUCAS AND W. BAUMGARTEN, *J. Am. Chem. Soc.*, 63 (1941) 1653–1657.
5 V. I. SHVETS, B. A. KLYASHCHITSKII, A. E. STEPANOV, AND R. P. EVSTIGNEEVA, *Tetrahedron*, 29 (1971) 331–340.
6 P. J. GAREGG, B. LINDBERG, I. KVARNSTRÖM, AND S. C. T. SVENSSON, *Carbohydr. Res.*, 139 (1985) 209–215.
7 H. O. BORÉN, P. J. GAREGG, L. KENNE, L. MARON, AND S. SVENSSON, *Acta Chem. Scand.*, 26 (1972) 644–652.
8 C. AUGÉ, S. DAVID, AND A. VEYRIÈRES, *J. Chem. Soc., Chem. Commun.*, (1976) 375–376.
9 M. A. NASHED AND L. ANDERSON, *Tetrahedron Lett.*, (1976) 3503–3506.
10 S. J. ANGYAL, G. C. IRVING, V. D. RUTHERFORD, AND M. E. TATE, *J. Chem. Soc.*, (1965) 6662–6664.
11 S. J. ANGYAL, M. E. TATE, AND S. D. GERO, *J. Chem. Soc.*, (1961) 4116–4122.
12 S. J. ANGYAL AND M. E. TATE, *J. Chem. Soc.*, (1965) 6949–6955.
13 S. J. ANGYAL AND R. M. HOSKINSON, *J. Chem. Soc.*, (1963) 2043–2047.
14 P. J. GAREGG, H. HULTBERG, AND S. WALLIN, *Carbohydr. Res.*, 108 (1982) 97–101.
15 T. SUAMI, S. OGAWA, K. OHASHI, AND S. OKI, *Bull. Chem. Soc. Jpn.*, 45 (1972) 3660–3667.