Carbohydrate Research, 207 (1990) 249–257
Elsevier Science Publishers B.V., Amsterdam

Improved preparation of acetals of *myo*-inositol and its (±)-1-benzyl ether: conformational analysis of di-*O*-isopropylidene-*myo*-inositol derivatives

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(Received December 13th, 1989; accepted for publication, March 1st, 1990)

ABSTRACT

The acid-catalysed reactions of *myo*-inositol with 3–5 equiv. of 2-methoxypropene or 2,2-dimethoxypropane in methyl sulfoxide or *N,N*-dimethylformamide gave mixtures of the 1,2:4,5-, 1,2:5,6-, and 1,2:3,4-di-*O*-isopropylidene derivatives with little or none of the 1,2:3,4:5,6-triacetal **5**. With ~7 equiv. of 2-methoxypropene in methyl sulfoxide–hexane, 70% of **5** was obtained. Kinetic acetonation of 1-*O*-benzyl-*myo*-inositol gave mainly the 3,4:5,6-diacetal, whereas thermodynamic conditions gave mainly the 2,3:5,6-diacetal. 1-*O*-Benzyl-2,3:4,5-di-*O*-isopropylidene-*myo*-inositol, obtained as a minor product, exists primarily in a chair conformation in non-polar solvents and in a skew-boat conformation in polar solvents, whereas the 6-acetate adopted only a skew-boat conformation.

INTRODUCTION

Recent advances in biochemical research[1] have led to a renewed interest in inositol phosphate chemistry[2] and have increased the need for efficient routes of synthesis to appropriately functionalised starting materials. The synthesis of selectively protected *myo*-inositol derivatives has involved di-*O*-cyclohexylidene[4] and di-*O*-isopropylidene[5] derivatives. Our studies of the acetonation of carbohydrates under kinetic control[6] prompted an investigation of the reaction of *myo*-inositol (**1**) and 1-*O*-benzyl-*myo*-inositol (**16**) with 2-methoxypropene under conditions of acid catalysis milder than those previously published, and these results are now reported.

RESULTS AND DISCUSSION

Treatment of *myo*-inositol (**1**) with 5 equiv. of 2-methoxypropene in methyl sulfoxide in the presence of a catalytic amount of toluene-*p*-sulfonic acid (Table I, entry 1) gave 90% of a mixture of 1,2:4,5- (**2**), 1,2:5,6- (**3**), and 1,2:3,4-di-*O*-isopropylidene-*myo*-inositol (**4**), and 1,2:3,4:5,6-tri-*O*-isopropylidene-*myo*-inositol (**5**). Column chromatography of the mixture gave **5**, and **2** and **3** were obtained by fractional crystallisa-

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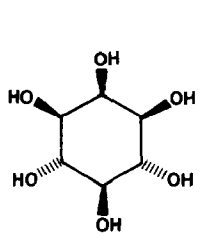
0008-6215/90/$ 03.50

tion and characterised as the corresponding diacetates **6** and **7**. With a shorter reaction time and a lower proportion of reagent (entry 2), **5** was not formed but benzoylation of the mixture of products gave 37% of the dibenzoate (**9**) of the 1,2:4,5-diacetal, which constitutes an improved preparation of this useful compound. The use of *N,N*-dimethylformamide (entries 3 and 4), regardless of the proportion of reagent employed, slightly favoured formation of the diacetal **3** relative to **2**. The preparation of the triacetal **5** in high yield (entry 5) was achieved with ~7 equiv. of 2-methoxypropene in methyl sulfoxide–hexane. The assignment of structures to **2** and **3** was based on spectral and physical data[5,7] together with those for the diacetates **6** and **7**, and the dibenzoate **9** (ref. 5). Compound **4** was characterised after allylation of the mixture of products (entry 3), followed by chromatography, which gave **12** (40% from *myo*-inositol), **13** (30%), and **14** (16%). Hydrolysis of **14** gave the known[7] tetrol **15**.

The acid-catalysed reaction of 1-*O*-benzyl-*myo*-inositol[8] (**16**) with 2-methoxypropene in *N,N*-dimethylformamide gave a mixture of the 2,3:4,5- (**18**, 27%) and the 3,4:5,6-diacetal (**19**, 69%), whereas, with 2,2-dimethoxypropane in acetone, a mixture of the 2,3:5,6-diacetal **17** (47%) and **18** (26%) was obtained. Compounds **17** and **18** are



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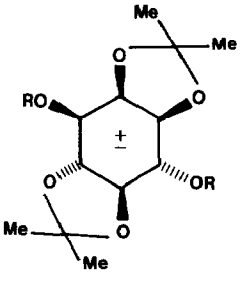
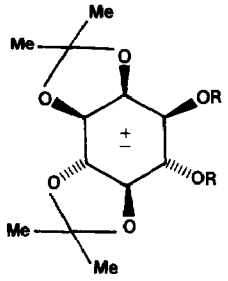
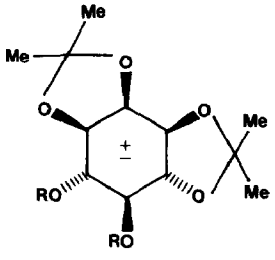


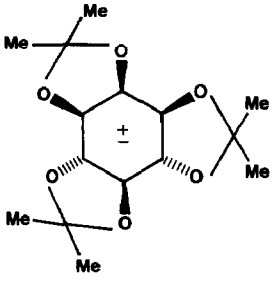
2 R = H
6 R = Ac
9 R = Bz
12 R = Allyl



3 R = H
7 R = Ac
10 R = Bz
13 R = Allyl



4 R = H
8 R = Ac
11 R = Bz
14 R = Allyl



5 R = H

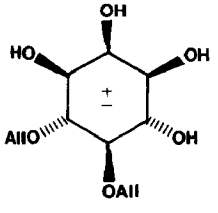


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TABLE I

Acetalation of *myo*-inositol[a]

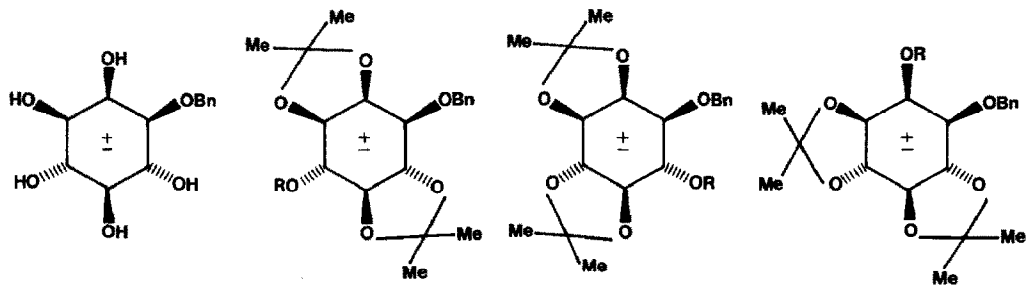
				Proportion of acetals[c]			
Entry	*Solvent*	*Time (h)*	*Yield*[b]	**2**	**3**	**4**	**5**
1[d]	Methyl sulfoxide	22	90	42	25	12	3
2	Methyl sulfoxide	2.5	90	47	29	14	
3	*N,N*-Dimethylformamide	7	92	42	33	17	
4[e]	*N,N*-Dimethylformamide	48	89	39	35	15	
5[f]	Methyl sulfoxide–hexane	26	70				70

[a] Reactions were carried out at room temperature with 3 equiv. of 2-methoxypropene unless otherwise noted. [b] Yield of the mixture of isomers. [c] Determined by ^{1}H-n.m.r. spectroscopy of the mixture. [d] Reaction with 5 equiv. of 2-methoxypropene. [e] Reaction with 3 equiv. of 2,2-dimethoxypropane. [f] Reaction with 7.2 equiv. of 2-methoxypropene.

convenient starting materials for the synthesis of 4- and 6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-*myo*-inositol 1-phosphate, which are considered to be fragments of lipid anchors[9]. Likewise, **19** can be used for the synthesis of 2-*O*-α-D-mannopyranosyl-*myo*-inositol 1-phosphate, which is a fragment of inositol-containing glycolipids of mycobacteria[10].

The assignment of structures to **17** and **19** based on the ^{1}H-n.m.r. data and those of the corresponding acetates (**20** and **22**) was straightforward. However, for **18**, there was a remarkable change in *J* values on acetylation (→**21**). The spectrum ($CDCl_3$) of **21** was complex due to extensive overlapping of peaks. These results, together with the unexpected formation of **19** in high yield, prompted an evaluation of the thermodynamic stability of **17**–**19**. The energy differences for the diacetals **17**–**19**, calculated according to MM2-programme[11], would account for a 9:1 mixture of **17** and **18** (ΔE 1.36 kcal/mol) with an insignificant amount of **19** (ΔE 3.71 kcal/mol). These results agree qualitatively with the experimental findings for acetalation under thermodynamic conditions, since the calculated energies are variable at least to ±0.5 kcal/mol.

The ^{1}H-n.m.r. data for **18** and **21** are recorded in Table II and the different *J* values



16 **17** R = H **18** R = H **19** R = H

20 R = Ac **21** R = Ac **22** R = Ac

TABLE II

^{1}H-N.m.r. data (δ, p.p.m.; J in Hz) for compounds **18** and **21** in different solvents

		Parameter											
Compound	*Solvent*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,1}$
18	Chloroform-*d*	3.57	4.38	4.19	3.78	3.31	4.10	4.4	5.3	8.6	10.1	9.9	7.3
	Benzene-d_6	4.11	3.44	4.17	3.31	4.23	4.08	4.2	5.2	8.8	10.2	8.1	6.0
	Acetone-d_6	3.68	4.54	4.33	3.98	3.45	4.04	4.1	6.4	7.9	10.4	8.4	4.1
	Methyl sulfoxide-d_6	3.65	4.52	4.35	3.90	3.46	3.9	4.1	6.3	7.9	10.5	8.4	4.3
21	Chloroform-*d*	–	–	–	–	3.60	5.25	–	–	–	–	8.1	2.5
	Benzene-d_6	3.65	4.08	4.29	4.68	3.64	5.60	3.8	7.2	7.4	10.8	8.0	2.0
	Acetone-d_6	3.74	4.51	4.42	4.17	3.72	5.23	3.8	6.7	7.5	10.7	8.4	3.4
	Methyl sulfoxide-d_6	3.74	4.48	4.31	3.90	3.64	5.11	4.0	6.2	7.9	10.4	9.0	5.0

TABLE III

Calculated proton–proton torsion angles and coupling constants for $^2C_5$ and $^1S_5$ conformers

	Angle (°)						*Coupling constant* (*Hz*)					
Conformer	*H-1/H-2*	*H-2/H-3*	*H-3/H-4*	*H-4/H-5*	*H-5/H-6*	*H-6/H-1*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,1}$
$^2C_5$	−45	40	−166	−177	178	170	4.2	4.9	8.5	9.8	9.9	8.8
$^1S_5$	55	−22	−153	−175	−152	93	2.9	7.0	6.7	9.9	6.5	0.7

Fig. 1. *A*, The $^2C_5$ chair conformer of 1-*O*-benzyl-2,3:4,5-di-*O*-isopropylidene-*myo*-inositol (**18**); and *B*, the skew conformer of the 6-acetate (**21**) of **18** according to MM2 calculations.

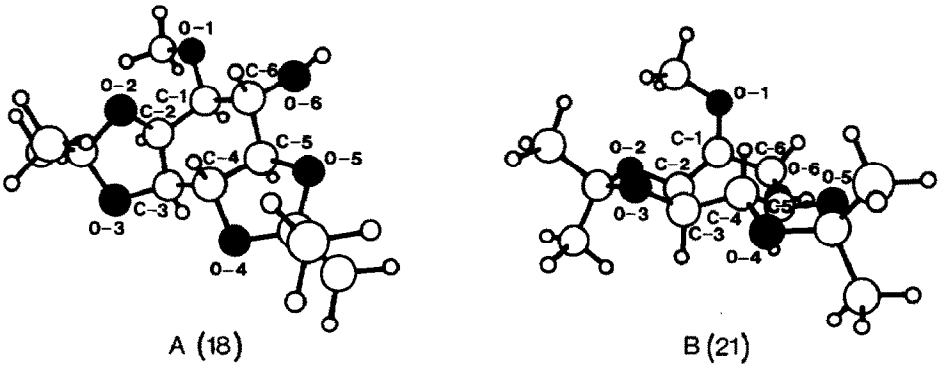


Fig. 1. *A*, The $^2C_5$ chair conformer of 1-*O*-benzyl-2,3:4,5-di-*O*-isopropylidene-*myo*-inositol (**18**); and *B*, the skew conformer of the 6-acetate (**21**) of **18** according to MM2 calculations.

indicate different conformations in solution. The *J* values were not affected appreciably ($\pm$0.5 Hz) by changes in temperature, but varied significantly with different solvents. MM2 calculations[11], carried out for **18** and **21** using the driver option of the programme, indicated the local minima for the $^2C_5$ chair and $^1S_5$ skew-boat conformations to have relative steric energies of 1.80 and 2.07 kcal/mol for **18** and **21**, respectively, taking the energy of the $^2C_5$ conformer as zero. However, the entropy term can be higher for a skew-boat than for a chair conformation and, therefore, the free energy difference between the $^2C_5$ and $^1S_5$ conformations could be smaller than calculated[12]. A view of the calculated chair and skew conformers is shown in Fig. 1.

The combination of force-field calculations and a Karplus-type equation has been used in the analysis of coupling constants[13]. The H/H torsion angles expected for the $^2C_5$ and $^1S_5$ forms are given in Table III along with the $^3J_{H,H}$ values calculated according to the equation proposed by Altona[14]. The observed *J* values for **18** could be accounted for by an almost exclusive $^2C_5$ conformation in chloroform-*d*, a $^2C_5$ conformation with a small proportion of the $^1S_5$ form in benzene-d_6, and a 1:1 mixture in acetone-d_6 or methyl sulfoxide-d_6. However, for **21**, the $^2S_5$ conformation would be the major one in benzene-d_6 or chloroform-*d*, and slightly preponderant in acetone-d_6, whereas in methyl sulfoxide-d_6 there would be a 1:1 mixture of $^2C_5$ and $^1S_5$ forms.

Thus, a higher proportion of chair conformers for **18** in non-polar solvents, with an important increase in the proportion of the skew-boat form in polar solvents and/or on acetylation, may be explained by the presence of an intramolecular hydrogen bond which stabilises the $^2C_5$ conformer in non-polar solvents. The occurrence of skew-boat forms in di-*O*-isopropylidene derivatives of *myo*-inositol has been deduced from i.r. data and also explained by the presence of intramolecular hydrogen bonding[15]. A non-chair conformation has been invoked to explain the *J* values of the di-*O*-isopropylidene derivatives of 3-deoxy-3-fluoro-4-*O*-methyl-*myo*-inositol[16]. The existence of these flexible forms could lead to misleading interpretations of isomer formation unless a rigorous analysis of the *J* values is carried out.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. T.l.c. was performed on Silica Gel GF_{254} (Merck) with detection by charring with sulfuric acid. Column chromatography was performed on Merck silica gel (70–230 mesh). ^{1}H-N.m.r. spectra were recorded with a Varian XL-300 or Bruker AM-200 instrument, and ^{13}C-n.m.r. spectra with a Varian XL-300, Bruker AM-200, or Bruker WP-80 spectrometer.

Acetonation of myo-*inositol.* — (*a*) A mixture of *myo*-inositol (**1**; 5 g, 27.78 mmol), methyl sulfoxide (125 mL), 2-methoxypropene (7.88 mL, 83.83 mmol), and toluene-*p*-sulfonic acid (500 mg) was stirred for 2.5 h at room temperature. More 2-methoxypropene (5.25 mL, 55.85 mmol) was added and the reaction was allowed to proceed for an additional 20 h. Triethylamine was added, the solvent was removed *in vacuo*, and the syrupy residue was chromatographed (1:1 hexane–ethyl acetate) to give **5** (0.93 g, 11%) and a 3.5:2:1 mixture (5.72 g, 79%) (^{1}H-n.m.r. data) of **2**–**4**.

1,2:3,4:5,6-Tri-*O*-isopropylidene-*myo*-inositol (**5**) had m.p. 220–221° (from hexane). ^{1}H-N.m.r. data: ^{1}H (300 MHz, benzene-d_6), δ 4.26 (dd, 1 H, $J_{1,2}$ 4.7, $J_{2,3}$ 3.3 Hz, H-2), 4.26 (t, 1 H, $J_{3,4} = J_{4,5} = 9.0$ Hz, H-4), 4.03 (dd, 1 H, $J_{1,2}$ 4.7, $J_{1,6}$ 9.0 Hz, H-1), 3.82 (t, 1 H, $J_{1,6} = J_{5,6} = 9.0$ Hz, H-6), 3.43 (t, 1 H, $J_{4,5} = J_{5,6} = 9.0$ Hz, H-5), 3.23 (dd, 1 H, $J_{2,3}$ 3.3, $J_{3,4}$ 9.0 Hz, H-3), 1.40 and 1.395 (2 s, 3 H each, 2 Me), 1.39 (s, 6 H, 2 Me), 1.37 and 1.20 (2 s, 3 H each, 2 Me); ^{13}C (20 MHz, chloroform-*d*), δ 112.7 (2 CMe_2), 112.3 (CMe_2), 82.3, 78.5, 76.7, 75.9, 74.3, 73.0, 28.7 (Me), 26.6 (3 Me), 26.4 and 26.1 (2 Me).

Anal. Calc. for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.10; H, 8.07.

1,2:4,5-Di-*O*-isopropylidene-*myo*-inositol (**2**) was purified by fractional recrystallisation (acetone–hexane) and had m.p. 166–168°; lit.[5] m.p. 171–173°. Acetylation of **2** gave the 3,6-diacetate **6**, m.p. 223–224°; lit.[5] m.p. 230–232°.

1,2:5,6-Di-*O*-isopropylidene-*myo*-inositol (**3**) was purified by column chromatography (hexane–ethyl acetate, 1:2) and had m.p. 169–170° (from acetone–hexane); lit.[7] m.p. 172–175°. Acetylation of **3** gave the 3,4-diacetate **7**, m.p. 160–163° (from ether); lit.[7] m.p. 165–168°.

Purification of the mixture of diacetals *via* the dibenzoates[7] afforded pure 1,2:3,4-di-*O*-isopropylidene-*myo*-inositol (**4**), which was characterised, *via* the di-*O*-allyl derivative **14**, as the tetrol **15**, m.p. 137–139°; lit.[7] m.p. 137–138°.

(*b*) Compound **1** (0.5 g, 2.78 mmol) was treated with 2-methoxypropene (0.79 mL, 8.38 mmol) and toluene-*p*-sulfonic acid (50 mg) in methyl sulfoxide (12.5 mL) for 3.5 h at room temperature. The mixture was neutralised with triethylamine and concentrated. Column chromatography (1:1 ethyl acetate–hexane) of the residue gave a mixture (0.65 g, 90%) of **2**–**4** in the ratios 3.5:2:1 (^{1}H-n.m.r. data). This mixture (300 mg, 1.15 mmol) was treated[5] with benzoyl chloride (1 mL) in pyridine (0.75 mL) at room temperature for 2 h. The product was collected and washed with pyridine and hexane to give pure 3,6-di-*O*-benzoyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**9**; 220 mg, 41%), m.p. 322–323°; lit.[5] m.p. 328°.

(*c*) Treatment of **1** (1.0 g, 5.56 mmol) in *N*,*N*-dimethylformamide (50 mL) with

2-methoxypropene (1.58 mL, 16.67 mmol) and toluene-*p*-sulfonic acid (100 mg) at room temperature for 7 h gave, after the usual work-up, a mixture (1.33 g, 92%) of **2–4** in the ratios 2.5:2:1. This mixture (1.20 g, 4.62 mmol) was treated[7] with allyl bromide (1.4 mL, 16.18 mmol) and sodium hydride (670 mg, 22.25 mmol) in *N,N*-dimethylformamide (30 mL) at room temperature for 2 h. Methanol (3 mL) and water (30 mL) were added, the mixture was extracted with ether (2 × 30 mL), and the combined extracts were dried and concentrated. Column chromatography (1:4 ethyl acetate–hexane) of the residue gave 3,4-di-*O*-allyl-1,2:5,6-di-*O*-isopropylidene-*myo*-inositol (**13**; 0.52 g, 30% from **1**), 5,6-di-*O*-allyl-1,2:3,4-di-*O*-isopropylidene-*myo*-inositol (**14**; 0.27 g, 16%), and 3,6-di-*O*-allyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**12**; 0.70 g, 40%), m.p. 81–82°; lit.[17] m.p. 85–87°.

(*d*) A mixture of **1** (0.5 g, 2.78 mmol), 2,2-dimethoxypropane (1.02 mL, 8.32 mmol), and toluene-*p*-sulfonic acid (50 mg) in *N,N*-dimethylformamide (25 mL) was stirred for 48 h at room temperature to give, after work-up, a mixture (0.64 g, 89%) of **2–4** in the ratios 2.5:2.5:1.

(*e*) A solution of **1** (1 g, 5.56 mmol) in methyl sulfoxide (4 mL) and hexane (20 mL) was treated with 2-methoxypropene (3.75 mL, 39.89 mmol) in the presence of toluene-*p*-sulfonic acid (60 mg) at room temperature for 24 h. The mixture was neutralised with triethylamine and the hexane layer was separated. Water (20 mL) was added to the methyl sulfoxide phase, the mixture was extracted with ether (2 × 25 mL), and the combined extracts were dried and concentrated to give 1,2:3,4:5,6-tri-*O*-isopropylidene-*myo*-inositol (**5**; 1.16 g, 70%).

*Acetonation of 1(3)-*O*-benzyl-*myo*-inositol* (**16**). — (*a*) A solution of **16** (135 mg, 0.05 mmol) in *N,N*-dimethylformamide (6 mL) was treated with 2-methoxypropene (0.17 mL, 1.81 mmol) and toluene-*p*-sulfonic acid (4 mg) for 3 h at 4°. The mixture was then neutralised (triethylamine), water was added, the mixture was extracted with ether (2 × 15 mL), and the combined extracts were dried and concentrated. Column chromatography (3:1 hexane–ethyl acetate) of the residue gave, first, **19** (119 mg, 69%) and then **18** (47 mg, 27%).

1-*O*-Benzyl-3,4:5,6-di-*O*-isopropylidene-*myo*-inositol (**19**) had m.p. 142–145°. N.m.r. data ($CDCl_3$): ^1H (300 MHz), δ 7.42–7.32 (5 H, Ph), 4.91 (d, 1 H, CH_2Ph), 4.69 (d, 1 H, CH_2Ph), 4.41 (bs, 1 H, H-2), 4.18 (dd, 1 H, $J_{3,4}$ 9.3, $J_{4,5}$ 9.6 Hz, H-4), 3.99 (dd, 1 H, $J_{5,6}$ 8.8, $J_{1,6}$ 10.1 Hz, H-6), 3.70 (dd, 1 H, $J_{1,2}$ 3.0, $J_{2,3}$ 10.2 Hz, H-1), 3.59 (dd, 1 H, $J_{4,5}$ 9.8, $J_{5,6}$ 8.9 Hz, H-5), 3.40 (dd, 1 H, $J_{2,3}$ 2.0, $J_{3,4}$ 8.8 Hz, H-3), 2.45 (s, 1 H, HO-2), 1.50, 1.49, 1.48, and 1.45 (4 s, 3 H each, 4 Me); ^{13}C (50 MHz), δ 137.7 (*C*-ipso), 128.5, 128.0, and 127.9 (aromatic), 112.9 and 112.4 (2 C, Me_2), 79.6, 79.3, 76.8, 76.5, 73.6, 72.0, 66.9, 26.8 (Me), 26.7 (2 Me), and 26.4 (Me).

Anal. Calc. for $C_{19}H_{26}O_6$: C, 65.16; H, 7.48. Found: C, 65.46; H, 7.51.

Acetylation of **19** gave the 2-acetate **22**, m.p. 138–142° (from hexane). ^1H-N.m.r. data (200 MHz, $CDCl_3$): δ 7.36–7.31 (m, 5 H, Ph), 5.87 (dd, 1 H, $J_{2,3}$ 2.5, $J_{1,2}$ 3.0 Hz, H-2), 4.74 (d, 1 H, CH_2Ph), 4.64 (d, 1 H, CH_2Ph), 4.06 (dd, 1 H, $J_{3,4}$ 9.3, $J_{4,5}$ 10.0 Hz, H-4), 3.90 (dd, 1 H, $J_{5,6}$ 8.3, $J_{1,6}$ 10.5 Hz, H-6), 3.78 (dd, 1 H, $J_{1,2}$ 3.0, $J_{1,6}$ 10.5 Hz, H-1), 3.59 (dd, 1 H, $J_{5,6}$ 8.3, $J_{4,5}$ 10.0 Hz, H-5), 3.44 (dd, 1 H, $J_{2,3}$ 2.5, $J_{3,4}$ 9.3 Hz, H-3), 2.15 (s, 3 H, Ac), 1.50, 1.46, 1.43, and 1.42 (4 s, 3 H each, 4 Me).

Anal. Calc. for $C_{21}H_{28}O_7$: C, 64.27; H, 7.79. Found: C, 64.50; H, 8.00.

1-*O*-Benzyl-2,3:4,5-di-*O*-isopropylidene-*myo*-inositol (**18**) had m.p. 156–159°. N.m.r. data: ^{1}H (300 MHz, $CDCl_3$): δ 7.40–7.32 (m, 5 H, Ph), 4.80 (d, 1 H, CH_2Ph), 4.71 (d, 1 H, CH_2Ph), 4.39 (dd, 1 H, $J_{1,2}$ 4.4, $J_{2,3}$ 5.3 Hz, H-2), 4.20 (dd, 1 H, $J_{2,3}$ 5.3, $J_{3,4}$ 8.6 Hz, H-3), 4.10 (ddd, J 2.2, $J_{1,6}$ 7.3, $J_{5,6}$ 9.9 Hz, H-6), 3.78 (dd, 1 H, $J_{3,4}$ 8.6, $J_{4,5}$ 10.2 Hz, H-4), 3.58 (dd, 1 H, $J_{1,2}$ 4.4, $J_{1,6}$ 7.3 Hz, H-1), 3.31 (dd, 1 H, $J_{4,5}$ 10.0, $J_{5,6}$ 9.9 Hz, H-5), 2.47 (d, 1 H, J 2.2 Hz, HO-6), 1.57, 1.46, 1.44, and 1.36 (4 s, 3 H each, 4 Me); ^{13}C (75 MHz, acetone-d_6), 139.3, 128.3, 127.6, 127.4 (aromatic), 111.1 and 110.0 (2 C, Me_2), 82.4, 79.4, 78.1, 77.0, 75.2, 72.5, 72.1, 26.9, 26.7, 26.6, and 25.0 (4 Me).

Anal. Calc. for $C_{19}H_{26}O_6$: C, 65.16; H, 7.48. Found: C, 65.00; H, 7.54.

Acetylation of **18** gave the 6-acetate **21**. ^{1}H-N.m.r. data (200 MHz, benzene-d_6): 7.44–7.38 (m, 2 H, aromatic), 7.22–7.06 (m, 3 H, aromatic), 5.56 (dd, 1 H, $J_{1,6}$ 1.9, $J_{5,6}$ 8.0 Hz, H-6), 4.83 (d, 1 H, CH_2Ph), 4.73 (d, 1 H, CH_2Ph), 4.64 (dd, 1 H, $J_{3,4}$ 7.2, $J_{4,5}$ 10.8 Hz, H-4), 4.24 (t, 1 H, $J_{2,3} = J_{3,4}$ = 7.2 Hz, H-3), 4.04 (dd, 1 H, $J_{1,2}$ 3.8, $J_{2,3}$ 7.2 Hz, H-2), 3.61 (dd, 1 H, $J_{1,6}$ 1.9, $J_{1,2}$ 3.8 Hz, H-1), 3.60 (dd, 1 H, $J_{4,5}$ 10.8, $J_{5,6}$ 8.0 Hz, H-5), 1.55 (s, 3 H, Ac), 1.54, 1.38, 1.29, and 1.23 (4 s, 3 H each, 4 Me).

(*b*) Compound **16** (143 mg, 0.53 mmol), in dry acetone (20 mL), was treated with 2,2-dimethoxypropane (1.13 mL, 9.20 mmol) and toluene-*p*-sulfonic acid (10 mg) for 2 h at room temperature. The mixture was then neutralised and concentrated. Chromatography (3:1 hexane–ethyl acetate) of the residue gave **18** (49 mg, 27%) and **17** (87 mg, 47%).

1-*O*-Benzyl-2,3:5,6-di-*O*-isopropylidene-*myo*-inositol (**17**) had m.p. 167–170°; lit.[16] m.p. 169–170°. Acetylation of **17** gave the 4-acetate **20**, m.p. 183–185°. ^{1}H-N.m.r. (200 MHz, chloroform-*d*): δ 7.40–7.32 (m, 5 H, Ph), 5.26 (dd, 1 H, $J_{3,4}$ 7.0 $J_{4,5}$ 11.1 Hz, H-4), 4.91 (d, 1 H, CH_2Ph), 4.79 (d, 1 H, CH_2Ph), 4.31 (dd, 1 H, $J_{1,2}$ 4.2, $J_{2,3}$ 4.7 Hz, H-2), 4.14 (dd, 1 H, $J_{1,6}$ 10.1, $J_{5,6}$ 9.2 Hz, H-6), 4.02 (dd, 1 H, $J_{2,3}$ 4.7, $J_{3,4}$ 7.0 Hz, H-3), 3.78 (dd, 1 H, $J_{1,2}$ 4.2, $J_{1,6}$ 10.1 Hz, H-1), 3.34 (dd, 1 H, $J_{4,5}$ 11.1, $J_{5,6}$ 9.2 Hz, H-5), 2.11 (s, 3 H, Ac), 1.60, 1.48, 1.44, and 1.33 (4 s, 3 H each, 4 Me).

Anal. Calc. for $C_{21}H_{28}O_7$: C, 64.28; H, 7.14. Found: C, 64.14; H, 7.44.

ACKNOWLEDGMENTS

This research was supported by the Ministerio de Educación y Ciencia (Grant PB 0367) and by Europharma S.A. The Ministerio de Educación y Ciencia is thanked for fellowships (to C. J. and A. Z.).

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