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SYNTHESIS OF THE ENANTIOMERIC 1,4,5,6-TETRA-*O*-BENZYL-*myo*-INOSITOLS

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ABSTRACT

The synthesis of the optically pure 1,4,5,6-tetra-*O*-benzyl-*myo*-inositols was achieved in four steps *via* diastereomeric 2,3-*spiro*-acetals of *myo*-inositol with L- and D-camphor as the key intermediates. Camphor dimethyl acetal was used for the acetalation reaction. The diastereomers were benzylated and separated by chromatography, and the structures of the products were determined by 2D-NOESY ^{1}H-n.m.r. spectroscopy. Hydrolysis of the diastereomers then afforded the title products.

INTRODUCTION

The synthesis of optically active derivatives of *myo*-inositol has attracted attention due to the interest in natural inositol phospholipids and *myo*-inositol phosphates in the second messenger pathways in the control of cell physiology[1–11]. The strategy for the synthesis of optically active 1,4,5,6-protected *myo*-inositols, intermediates in the synthesis of phosphatidyl inositol, involves the preparation of the racemic 1,4,5,6-tetra-*O*-benzyl- and 4,5-di-*O*-allyl-1,6-di-*O*-benzyl-*myo*-inositols, derivatization with a chiral agent, isolation of the resulting diastereomers by chromatography, and removal of the chiral auxiliary[2,3,9]. The resolution of substituted diols into enantiomers *via* the formation of cyclic acetals with D-camphoroquinone has been described recently[12]. We now report a new method for the synthesis of optically pure 1,4,5,6-tetra-*O*-benzyl-*myo*-inositol, in which cyclic acetals derived from D- or L-camphor were the key intermediates.

RESULTS AND DISCUSSION

Treatment of *myo*-inositol (**1**) with a 2-fold molar excess of D-camphor dimethyl acetal (**2**) in anhydrous methyl sulfoxide at 68–70° in the presence of a catalytic amount of sulfuric acid gave a mixture of positional and stereoisomers as

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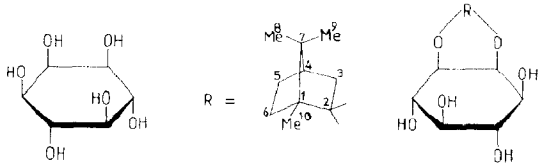
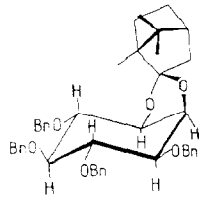


1 2 3

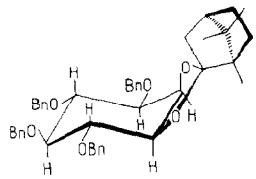
judged by the complex ^{13}C-n.m.r. spectra. Attempts to obtain good yields of the mono-acetal were not successful. The above mixture was partially hydrolysed in the presence of *p*-toluenesulfonic acid at room temperature to give a mixture of four diastereomeric 2,3-acetal derivatives **3**. Attempts to separate the components by chromatography and crystallization failed.

The dry mixture of tetraols **3** was treated with benzyl bromide in the presence of sodium hydride at 80° in 6:1 toluene–hexamethylphosphoramide, to give 90% of the tetra-*O*-benzyl derivatives **4a–d**. H.p.t.l.c. (benzene–di-isopropyl ether, 100:1) of the mixture revealed **4a–d** (mobilities 0.14, 0.21, 0.27, and 0.30) to be in the ratios 47:23:13:17 based on the integrated intensities of signals (δ 1.08, 1.07, 1.025, 1.048) of the methyl group at position 9 of the camphor moiety in the ^1H-n.m.r. spectrum. The isomers **4a** and **4b** were isolated by chromatography on silica gel (hexane–ether, 6:1), while **4c** and **4d** were obtained as a mixture.

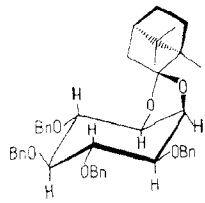
Hydrogenolysis of **4a** in ethanol over Pd/C afforded a single isomer of **3**, which was stable under neutral conditions but was epimerized easily in the presence of a small amount of *p*-toluenesulfonic acid in methanol at room temperature to give a 1:1 mixture of two isomers **3** configurationally related to **4a** and **4d**. Extension of the reaction time resulted in the formation of considerable amounts of two other isomers of **3** and of *myo*-inositol. The configurations of the tetraols **3** resulting from isomerisation were verified by rebenzylation to give **4**. Likewise, hydrogenolysis of



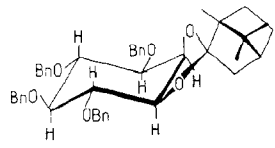
4a



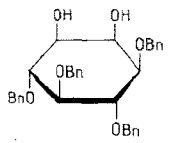
4b



4c



4d



5a,b

4b yielded a tetraol **3**, which could be epimerized into a mixture of two isomers related to **4b** and **4c**. Thus, it appears that the isomerization involves cleavage of the *endo* C–O bond in the cyclic acetal followed by *exo*-attack by HO-3. The tetraols **3** formed by hydrolysis of the crude product of the acetalation reaction precipitated from the reaction medium, thus avoiding equilibration. It is concluded that the composition of product mixture **4a–d** is kinetically controlled.

Hydrolysis of **4a** at 100° in aqueous 80% acetic acid gave (+)-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol {**5a,** 88%, $[\alpha]_D^{20}$ +24° (chloroform)}. In a similar manner, the isomer **4b** afforded (−)-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol {**5b**, $[\alpha]_D^{20}$ −25° (chloroform)}. Hydrolysis of the mixture **4c,d** also yielded a (−)-tetra-*O*-benzyl-*myo*-inositol, albeit with a low $[\alpha]_D^{20}$ value (−6.25°). The starting material suitable for the synthesis of natural phosphatidyl inositol is (−)-**5b**, which was produced in quantities smaller than that of (+)-**5b**. Therefore, the synthesis was repeated using L-camphor dimethyl acetal. The hydrolysis of the least mobile diastereomer (**4e**, enantiomeric to **4a**) afforded **5b** ($[\alpha]_D^{20}$ −23°).

The diastereomers **4a–4d** differ in the configurations of the *myo*-inositol moieties and in the orientations of the camphor residues. Since, in the mixture **4c** + **4d**, **4d** preponderates and the product of the hydrolysis of **4c** + **4d** was (−)-tetra-*O*-benzyl-*myo*-inositol (see below), it appears that the configurations of the *myo*-inositol residues in **4b** and **4d** are identical, as are those of **4a** and **4c**.

The exo/endo geometry (relative to O-1 of the *myo*-inositol moiety) in the cyclic acetals **4** was determined by 2D-NOESY ^{1}H-n.m.r. spectroscopy. The four possible structures **4a–d** are shown in the formula. Expansions of the 2D-NOESY spectra of isomers **4a, 4b**, and of the mixture **4c,d** are shown in Fig. 1. The structure assigned to **4a** is indicated by the cross-peaks arising from the Me-10 in the camphor moiety and H-4 and H-6 of *myo*-inositol (Fig. 1a). Likewise, the cross-peaks for **4b** result from Me-10 of the camphor moiety and H-2 of the *myo*-inositol (Fig. 1b). Interpretation of the spectrum of the mixture **4c,d** required prior assignments of the sets of methyl and inositol signals. The assignments of the methyl signals, as shown in Fig. 1c, were based on the difference in their integrated intensities coupled to the difference in the yield of **4c** and **4d**, and that of the *myo*-inositol residue was aided by a ^{1}H–^{1}H COSY spectrum (not shown). In the NOESY spectrum (Fig. 1c), the signal from Me-10 of **4c** (at 0.799 p.p.m.) was correlated with signals for H-1 and H-2, while the corresponding signal for **4d** (at 0.862 p.p.m.) was correlated with the signal for H-6. Therefore, the most likely structures of **4c** and **4d** are as depicted.

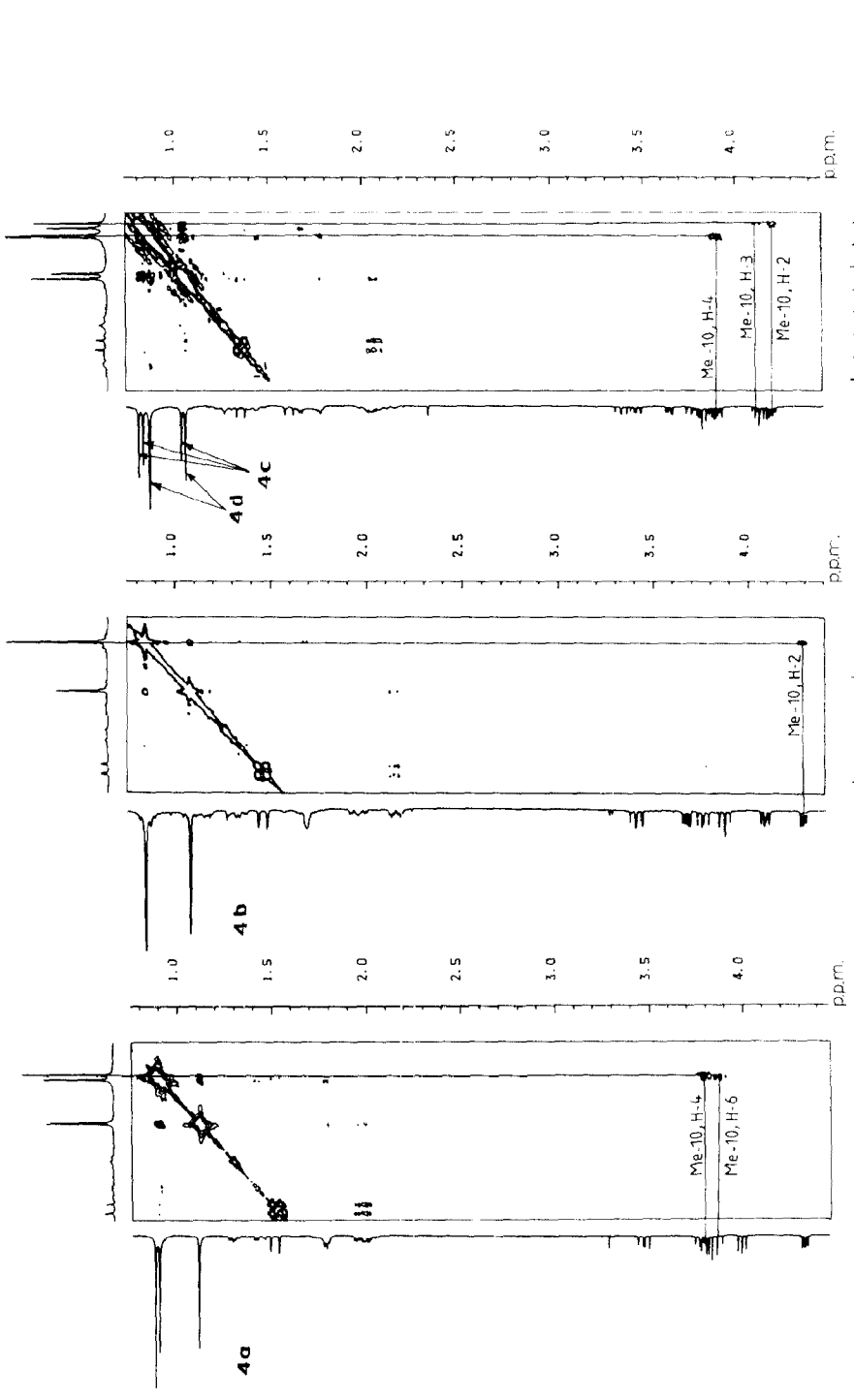


Fig. 1. Partial 2D-NOESY spectra of **4a–d** in $CDCl_3$ (20–50 mg of **4** in 0.5 mL of $CDCl_3$); proton, 90°; pulse, 9.5 μs; mixing time, 750 ms; scan recycle time, 3 s.

The advantage of the synthesis described lies in the asymmetric induction observed during the formation of the cyclic acetal derivatives **3**. Despite the fact that all four possible stereoisomers are formed, the desired compound is produced in major proportion (~50%) and is readily isolable.

EXPERIMENTAL

myo-Inositol, D-camphor, trimethyl orthoformate, benzyl bromide, and (−)-borneol were commercial products. L-Camphor {$[\alpha]_D^{20}$ −40° (chloroform)} was obtained by oxidation of (−)-borneol with potassium dichromate in the presence of sulfuric acid[14]. Dimethyl acetals of D- or L-camphor were obtained by their reactions[15,16] with trimethyl orthoformate. Reactions were monitored by t.l.c. on silica gel (Merck). The purity of each product was checked by h.p.t.l.c. (Merck, 5547) and also by ^{1}H- and ^{13}C-n.m.r. spectroscopy. All n.m.r. spectra (external Me_4Si) were recorded with a Bruker MSL-300 spectrometer (^{1}H, 300.13 MHz; ^{13}C, 75.47 MHz). Assignments of ^{13}C resonances were assisted by the DEPT technique and H–C COSY experiments. Optical rotations were measured with a Perkin–Elmer 241 MC spectropolarimeter.

Diastereomeric 2,3-O-(D-1,7,7-Trimethyl[2.2.1]bicyclohept-2-ylidene)-myo-inositols (**3**). — To a suspension of dry *myo*-inositol (1.9 g, 10.5 mmol) in anhydrous dimethyl sulfoxide (9 mL) was added D-camphor dimethyl acetal (3.9 g, ~2 equiv.). The mixture was warmed up to 68–70°, conc. sulfuric acid (50 μL) was added, and the mixture was kept at 68–70° until all of the *myo*-inositol had dissolved (2 h) and only a trace of monoacetal derivative could be detected by t.l.c. (chloroform–methanol, 10:1). Triethylamine (500 μL) was added and the mixture was concentrated under vacuum. Chloroform–methanol–water (5 mL, 90:10:2) containing *p*-toluenesulfonic acid (10 mg) was added to the residue, and the mixture was stirred at room temperature until the hydrolysis of the polyacetal derivatives was complete (1.5 h). Solid sodium carbonate (100 mg) was then added, the mixture was concentrated under vacuum, the residue was dried *in vacuo* at room temperature (1.5 h), and the crude **3** was used directly for the alkylation reaction.

1,4,5,6-Tetra-O-benzyl-2,3-O-(D-1,7,7-trimethyl[2.2.1]bicyclohept-2-ylidene)-myo-inositols (**4a** *and* **4b**). — The foregoing crude mixture of **3** was dispersed in anhydrous toluene (6 mL) by sonication (3 min), and anhydrous hexamethylphosphoramide (1.0 mL) and sodium hydride (2.1 g of a 50% suspension in mineral oil) were added. The dispersion was stirred at 70° until the evolution of hydrogen ceased, then treated with freshly distilled benzyl bromide (44.1 mmol, 7.5 g). Heating was continued for 4 h at 80°, water was added (40 mL), products were extracted with hexane, and the extract was concentrated. Column chromatography (silica gel, 6:1 hexane–ether) yielded fractions containing isomers **4a–4d**.

Compound **4a** (2.3 g, 33%) had $[\alpha]_D^{20}$ +18° (*c* 3, chloroform), R_F 0.14 (benzene–di-isopropyl ether, 100:1). N.m.r. data ($CDCl_3$): ^{13}C, δ 10.14, 20.40, 20.63 (Me-8,9,10), 27.08, 29.81 (CH_2-5,6), 44.94 (CH_2-3), 45.25 (CH-4), 47.99,

51.58 (C-1,7), 72.47, 73.89, 74.92, 75.08 (PhCH$_2$), 73.72, 76.25, 77.42, 80.70, 82.19, 83.22 (CH inositol), 117.70 (C-2), 127.53–128.30 (Ph, 5 lines), 138.51–138.85 (Ph, 4 lines); ^{1}H, δ 0.85 (s, 3 H, Mc-10), 0.88 (s, 3 H, Me-8), 1.08 (s, 3 H, Me-9), 1.20–2.02 (m, ~7 H), 3.78 (dd, 1 H, $J_{1,2}$ 4.0 Hz, H-1), 4.30 (dd, 1 H, $J_{2,3}$ 6.1 Hz, H-2), 3.96 (dd, 1 H, $J_{3,4}$ 7.1 Hz, H-3), 3.73 (dd, 1 H, $J_{4,5}$ 9.6 Hz, H-4), 3.43 (dd, 1 H, $J_{5,6}$ 7.8 Hz, H-5), 3.83 (dd, 1 H, $J_{6,1}$ 8.7 Hz, H-6), 4.33–4.92 (m, 8 H, 4 PhCH_2), 7.24–7.40 (m, 20 H, 4 Ph).

Anal. Calc. for $C_{44}H_{50}O_6$: C, 78.23; H, 7.47. Found: C, 77.68; H, 7.60.

Compound **4b** (820 mg, 12%) had $[\alpha]_D^{20}$ −27° (*c* 4.5, chloroform), R_F 0.24. N.m.r. data ($CDCl_3$): ^{13}C, δ 10.85, 21.11, 21.23 (Me-8,9,10), 27.61, 29.37 (CH_2-5,6), 45.76 (CH_2-3), 46.75 (CH-4), 48.57, 54.37 (C-1,7), 72.81, 75.34, 75.81, 76.16 (PhCH$_2$), 74.67, 78.67, 79.53, 81.55, 82.26, 82.94 (CH inositol), 119.18 (C-2), 128.18–129.04 (Ph, 9 lines), 139.15–139.56 (Ph, 4 lines); ^{1}H, δ 0.83 (s, 6 H, Me-10, Me-8), 1.07 (s, 3 H, Me-9), 1.1–2.17 (m, ~7 H), 3.66 (dd, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.28 (dd, 1 H, $J_{2,3}$ 5.4 Hz, H-2), 4.08 (dd, 1 H, $J_{3,4}$ 7.3 Hz, H-3), 3.75 (dd, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 3.40 (dd, 1 H, $J_{5,6}$ 8.8 Hz, H-5), 3.86 (t, 1 H, $J_{6,1}$ 8.6 Hz, H-6), 4.65–4.94 (m, 8 H, 4 PhCH_2), 7.24–7.41 (m, 20 H, 4 Ph).

Anal. Calc. for $C_{44}H_{50}O_6$: C, 78.23; H, 7.47. Found: C, 77.88; H, 7.73.

The mixture **4c** + **4d** (1.35 g, 19%) had $[\alpha]_D^{20}$ −1.9° (*c* 5.9, chloroform). Compound **4c**, ^{1}H-n.m.r. data ($CDCl_3$): δ 0.799 (s, Me-10), 0.830 (s, Me-8), 1.025 (s, Me-9), 1.17–2.20 (overlapped resonances from camphor of **4c** and **4d**), 3.638 (dd, $J_{1,2}$ 3.8 Hz, H-1), 4.197 (dd, $J_{2,3}$ 5.4 Hz, H-2), 4.105 (dd, $J_{3,4}$ 7.1 Hz, H-3), 3.754 (dd, $J_{4,5}$ 10.0 Hz, H-4), 3.377 (dd, $J_{5,6}$ 8.7 Hz, H-5), 3.88 (t, $J_{6,1}$ 8.7 Hz, H-6), 4.62–4.94 (m, PhCH_2, overlapped resonances from **4c** and **4d**), 7.23–7.41 (m, Ph).

Compound **4d**, ^{1}H-n.m.r. data ($CDCl_3$): δ 0.862, 0.870 (s, Me-10 and Me-8), 1.048 (s, Me-9), 1.17–2.20 (overlapped resonances from camphor of **4c** and **4d**), 3.799 (dd, $J_{1,2}$ 3.7 Hz, H-1), 4.182 (dd, $J_{2,3}$ 6.8 Hz, H-2), 4.124 (dd, $J_{3,4}$ 6.7 Hz, H-3), 3.891 (dd, $J_{4,5}$ 9.7 Hz, H-4), 3.456 (dd, $J_{5,6}$ 7.9 Hz, H-5), 3.820 (dd, $J_{6,1}$ 7.2 Hz, H-6), 4.62–4.94 (m, PhCH_2), 7.23–7.41 (m, Ph).

*1,4,5,6-Tetra-*O*-benzyl-*myo*-inositols* (**5a** *and* **5b**). — Compounds **4a** and **4b** (100 mg) were each suspended in aqueous 80% acetic acid (5 mL). Each suspension was kept at 100° for 2 h. When the reaction was complete (t.l.c., 4:1 hexane–ether), the solvents were evaporated under reduced pressure. Column chromatography (silica gel, 50:1 chloroform–acetone) of the residue yielded **5a** or **5b** (70 mg, 88%). Larger quantities of **5** were purified by crystallization from hexane–benzene (2:1).

Compound **5a** had m.p. 141–143°, $[\alpha]_D^{20}$ +24° (*c* 2.7, chloroform) (lit.[17] m.p. 140–142°, $[\alpha]_D^{20}$ +25°); R_F 0.42 (chloroform–acetone, 10:1). N.m.r. data ($CDCl_3$): ^{1}H δ 3.42–3.51 (m, 3 H), 3.82 [t, 1 H, $J_{6,5} = J_{6,1} = 9.4$ Hz, H-6(4)], 3.98 [t, 1 H, $J_{4,5} = J_{4,3} = 9.4$ Hz, H-4(6)], 4.20 (t, 1 H, $J_{2,1} = J_{2,3} = 3.0$ Hz, H-2), 4.20–4.96 (m, 8 H, 4 PhCH_2), 7.25–7.38 (m, 20 H, 4 Ph); ^{13}C δ 69.30, 71.89, 80.14, 81.42, 81.69, 83.26 (CH inositol), 72.79, 75.56, 75.65, 75.87 (PhCH$_2$), 127.55–128.53 (Ph, 5 lines), 137.88, 138.62, 138.75 Ph).

Compound **5b**, m.p. 140–142°, $[\alpha]_D^{20}$ −25° (*c* 2.7, chloroform); lit.[17] $[\alpha]_D^{20}$ −24°.

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