Synthesis of some Deoxy-fluoro Analogues of *myo*-Inositol

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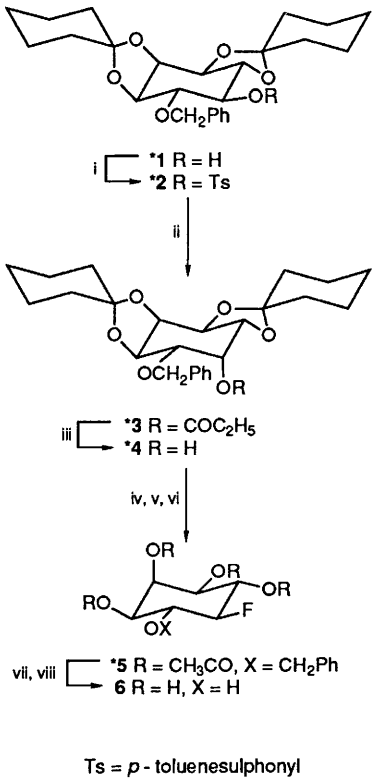
Syntheses of 5-deoxy-5-fluoro-*myo*-inositol and optically pure 1-L- and 1-D-1-deoxy-1-fluoro-1-fluoro-*myo*-inositol from *myo*-inositol are reported as being formed in high yield.

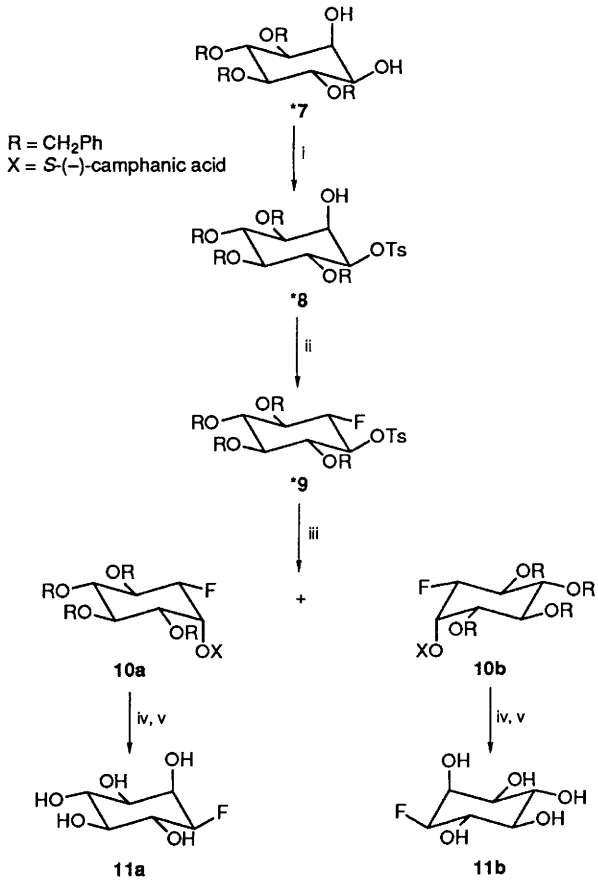
The inositol lipids are membrane constituents that have a number of important cellular functions: they are involved in the anchoring of membrane proteins,[1] secretion[2] and in cell signalling.[3] Most attention has focused on the role of inositol lipids in cell signalling and some of the key steps involved in this pathway are established. The hydrolysis of one of the inositol lipids, phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)P_2], has been shown to be an early event in response to activation of a wide variety of receptors. The products of PtdIns(4,5)P_2 hydrolysis, inositol 1,4,5-trisphosphate [Ins(1,4,5)P_3] and diacylglycerol both act as second messengers. Ins(1,4,5)P_3 releases Ca^{2+} from intracellular stores and causes a rise in cytosolic Ca^{2+} and diacylglycerol is an activator of protein kinase C. Another inositol phospholipid, phosphatidylinositol 3-phosphate (PtdIns3P) of unknown function, has recently been characterised.[4,5] Substrate analogues or inhibitors of the enzymes that synthesise the inositol lipids would be useful to determine the cellular functions of the lipids, but no specific inhibitors have yet been identified.

We have synthesised analogues of *myo*-inositol, in which single hydroxy groups have been replaced by fluorine to give derivatives with the same stereochemistry as *myo*-inositol,[6,7,8] in order to determine whether they act as substrates or inhibitors of the enzymes involved in inositol lipid synthesis. This required the development of efficient syntheses for these materials so that they are available in practical yields from convenient starting materials.

For the synthesis of the *meso*-compound 5-deoxy-5-fluoro-*myo*-inositol, 6-*O*-benzyl-1,2:3,4-di-*O*-cyclohexylidene-*myo*-inositol, **1** was chosen as the starting material. This crystalline compound was obtained in two steps from *myo*-inositol by the method of Garegg and Lindberg,[9] in good yield. Fluorination with diethylaminosulphur trifluoride (DAST) usually occurs with Walden inversion, so if the product is to possess the desired *myo*-configuration, an additional inversion step is required in the synthesis. Inversion of the 5-position was achieved by tosylation of the free 5-hydroxy group and treatment of the product with caesium propionate in *N,N*-dimethylformamide (DMF) to give the *neo*-inositol derivative **3**.[10] The hydroxy group was recovered by base hydrolysis of



Scheme 1 Synthesis of 5-deoxy-5-fluoro-*myo*-inositol. *Reagents*: i, *p*-toluenesulphonyl chloride, pyridine; ii, caesium propionate, DMF; iii, CH_3OH, NaOH; iv, DAST; v, CH_3CO_2H, H_2O; vi, $(CH_3CO)_2O$, pyridine; vii, H_2, Pd/C; viii, catalytic $NaOCH_3$, CH_3OH.* Racemic compound; only one enantiomer shown



Scheme 2 Synthesis of 1-D- and 1-L-1-deoxy-1-fluoro-*myo*-inositol. *Reagents*: i, *p*-toluenesulphonyl chloride, pyridine; ii, DAST; iii, *S*-(−)-caesium camphanate; iv, CH_3OH, NaOH; v, H_2, Pd/C. * Racemic compound; only one enantiomer shown

the propionyl group to give **4**, which when mixed with DAST gave a fluorine derivative with the required *myo*-configuration. The acid labile cyclohexylidene groups were removed and replaced by acetates in two steps, which simplified purification and subsequent handling of the material. The configuration of **5** was assigned through ring proton coupling constants in the ^{1}H NMR spectrum. Deprotection of **5** was carried out in two steps: first the benzyl group was removed by hydrogenation over a catalyst in weakly acidic solvent and the product of this was then deacylated by treatment with catalytic amounts of sodium methoxide in methanol to give **6**. The final product was purified for biological experiments by neutralising it on a mixed bed resin and recrystallising from ethanol. The yield of this product from **1** was 73%; all the steps proceeded in almost quantitative yield except fluorination, which was optimised at 85%.

An important consideration in the synthesis of the 1-derivatives is that the loss of the plane of symmetry between C–2 and C–5 in *myo*-inositol compounds results in the production of enantiomers that have to be resolved. Attempts at synthesising the 1-substituted compounds from cyclohexylidene protected inositol derivatives by first inverting the 1-position by nucleophilic displacement were unsuccessful, because this procedure gave an elimination product. These problems were solved as shown in Scheme 2 using the protected inositol **7**, firstly by carrying out the inversion necessary to recover the *myo*-configuration after the fluorination step in order to avoid possible elimination, and then by combining the inversion and resolution in a single step. The latter was achieved by using the optically active salt S-(−)-caesium camphanate. 1,4,5,6-Tetrabenzyl-*myo*-inositol **7**, available in three steps by the method of Gigg *et al.*,[11,12] was tosylated exclusively at the 3-position.[13] This compound was then fluorinated to give a *scyllo*-inositol derivative **9** in 85% yield. The *myo*-inositol configuration was recovered by displacement of the *p*-toluenesulphonate group by optically active camphanic acid in 90% yield. The two resulting diastereoisomers were separated by column chromatography on deactivated silica gel (CH_2Cl_2 : Et_2O 95 : 5 v/v). The same products were obtained by displacing the *p*-toluenesulphonate in **8** by caesium propionate, followed by base hydrolysis to recover the hydroxy group and then resolution with *S*-(−)-camphanic acid chloride. Deprotection was carried out in quantitative yield by base hydrolysis of the camphanate followed by hydrogenolysis of the benzyl protecting groups. Purification of **11a** and **11b** was carried out as described for **6**. The yield of each was between 70–75% of the theoretical maximum from **7**.†

The absolute configurations of the enantiomers of **11** were assigned on the assumption that the phosphatidylinositol synthetase would be able to use the 1-L **11b** but not the 1-D enantiomer **11a** of 1-deoxy-1-fluoro-*myo*-inositol as substrate, because in the biosynthesis of phosphatidylinositol the phosphatidyl group is attached exclusively to the 1-D-position of *myo*-inositol. The ^{3}H-labelled fluoro compounds were synthesised (to be described elsewhere) and the enantiomer that was incorporated into the cell lipid was, therefore, assigned as the 1-L-enantiomer. The enantiomer assigned on this basis, **11b** had the same sign of optical rotation as the published value for this compound.[7]

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† All new compounds reported gave satisfactory NMR spectra and elemental analysis, their melting points were as follows: **2** 127–130 °C; **3** syrup; **4** 200 °C; **5** 132 °C; **6** lit.[6] m.p. 222–224 °C; **9** 134–136 °C; **10a** 122–124 °C; **10b** 115 °C; **11a** 216–218 °C; **11b** 216–218 °C.