A Synthesis of (−)-1L-1-Deoxy-1-fluoro-*myo*-inositol; a Compound of Potential Use in sorting out the Phosphatidylinositol Response

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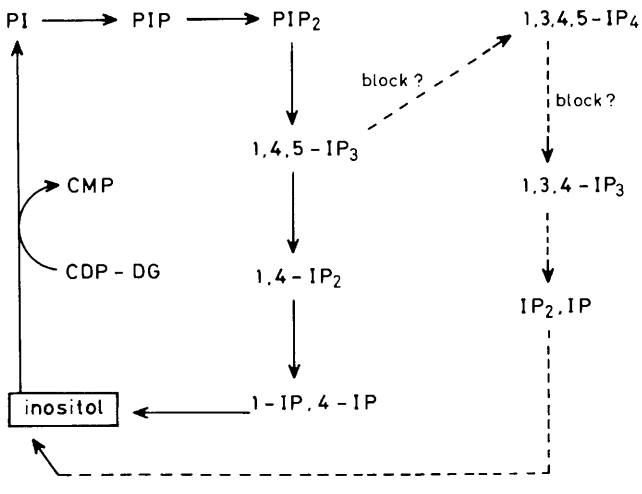
A synthesis of 1L-1-deoxy-1-fluoro-*myo*-inositol in optically pure form starting from *myo*-inositol is reported.

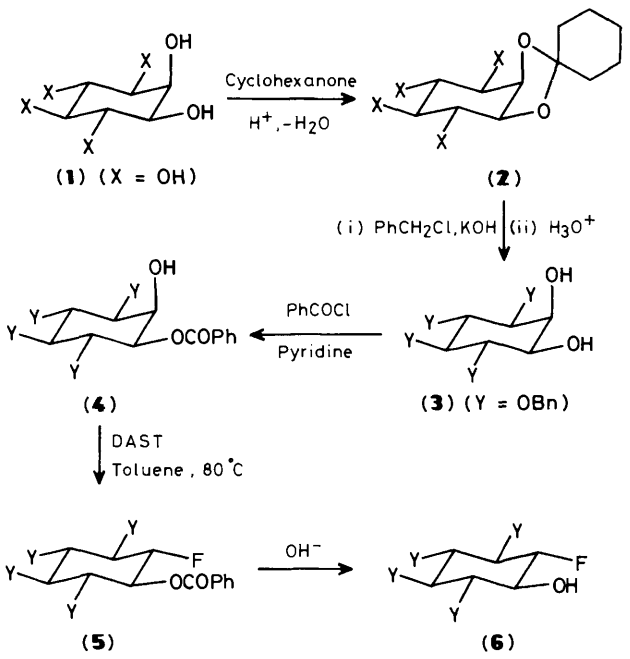
As part of an effort to elucidate the biological role of the various inositol phosphate derivatives generated in the response of a cell to a drug, hormone, or neuropeptide,[1] we have contemplated the construction of various unnatural inositol analogues. Specifically, we sought to prepare a compound which would preclude formation of both *myo*-inositol 1,3,4-trisphosphate (1,3,4-IP_3) and *myo*-inositol 1,3,4,5-tetrakisphosphate (1,3,4,5-IP_4), thus allowing a means of sorting out the relative importance of these compounds in the PI (phosphatidylinositol) response *vis-à-vis* 1,4,5-IP_3, a substance regarded as mobilizing calcium from the endoplasmic reticulum (Scheme 1).[1] Additionally, such analogues may prove useful in controlling abnormal conditions of cellular growth such as occur in cancer.

The true workability of such a notion would, of course, in the best of circumstances require that such an inositol analogue be incorporated in reasonable amounts into the cellular membrane. Upon consideration of the various tenets of drug design, we concluded that the best derivative to prepare would involve a simple isosteric replacement of the hydroxy-group at C-3 of *myo*-inositol by a fluorine atom.[2] Such an isosteric replacement was viewed as giving rise to a compound which in terms of its physiochemical properties should still be close enough to inositol to enter into the cell *via* a carrier-mediated process. Additionally, the fluorine atom still provides a site for acceptance of a hydrogen bond.[3]

myo-Inositol (**1**) was thus selectively converted into its 1,2-*O*-cyclohexylidene derivative (**2**) as described by Angyal (Scheme 2).[4] The resulting tetra-ol was next converted into 1,4,5,6-tetra-*O*-benzyl-*myo*-inositol (**3**) by benzylation fol-



Scheme 1. Selective blockade of the PI cycle (the cyclic inositol phosphates have been excluded).



Scheme 2. Synthesis of intermediate (**6**).[2]

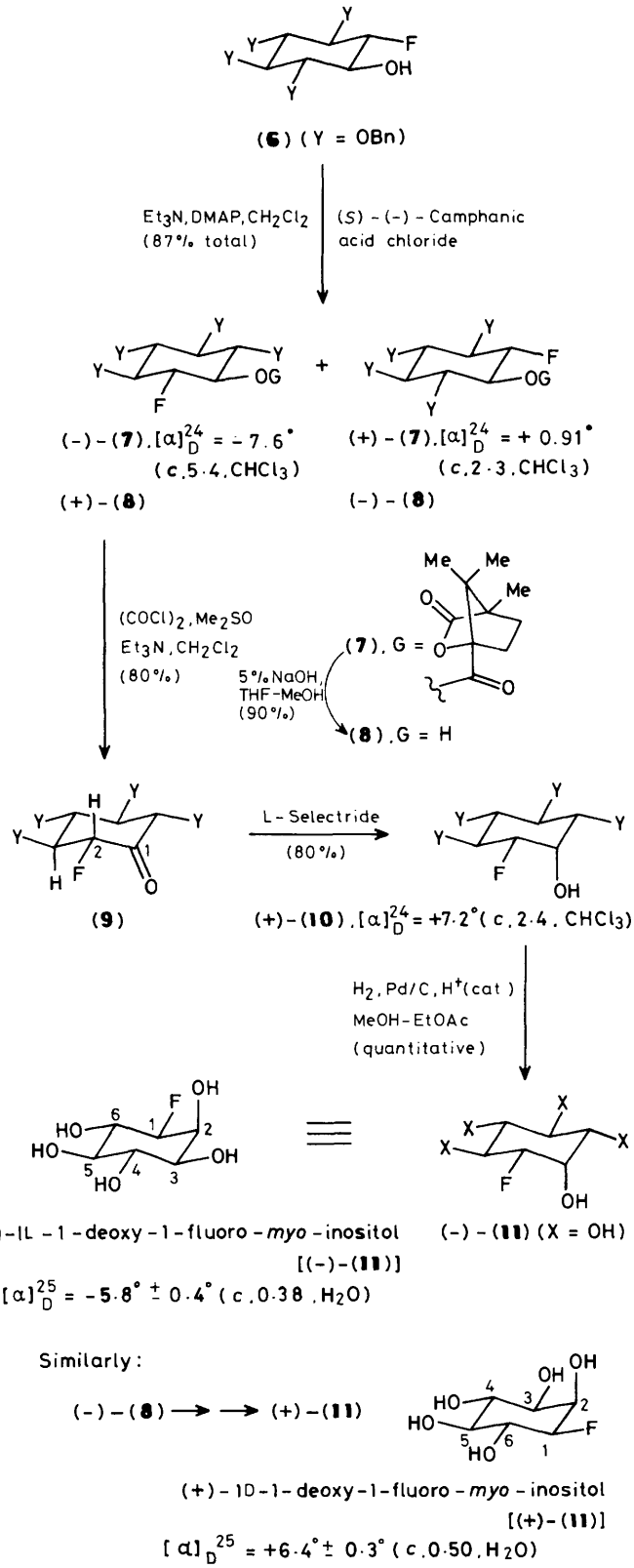
lowed by removal of the cyclohexylidene group. The equatorial hydroxy-group of the resulting diol was selectively benzoylated and the axial alcohol replaced by an equatorial fluorine atom by DAST (diethylaminosulphur trifluoride) treatment.[2,5]

The benzoyl group of (**5**) was cleaved by base treatment to provide the mono-alcohol (**6**). Resolution could be accomplished at this stage by chromatographic separation of the diastereoisomeric esters formed upon reaction of (**6**) with (*S*)-(−)-camphanic acid chloride (Scheme 3).[6] By carrying out a similar sequence of synthetic operations substituting the *p*-bromobenzyl group for the benzyl groups in compounds (**3**—**7**), we were able to obtain good crystals of one isomer of the tetrakis-(*p*-bromobenzyl) analogue of (+)-(**7**) {$[\alpha]_D^{24}$ = +0.92° (*c* 0.26, $CHCl_3$)} suitable for a single-crystal *X*-ray analysis. This *X*-ray analysis, in conjunction with chemical correlation studies, enabled us to assign the absolute stereochemistry to compounds (**7**—**11**).

To establish the axial hydroxy-group in the inositol isostere, the camphanic ester (**7**) was hydrolysed to alcohol (**8**), and a Swern oxidation process was brought about. The ^1H n.m.r. spectrum of ketone (**9**) exhibited a 9.8 Hz coupling constant for the C-2 proton, a *J*-value indicative of the *trans*-diaxial relationship between the C-2 proton and its vicinal proton neighbour. The ketone was reduced in turn to the axial alcohol (**10**) by L-Selectride.[7]

Lastly, the benzyl groups of (**10**) were removed by hydrogenolysis over Pd/C under mildly acidic conditions to provide the desired optically pure (−)-1L-1-deoxy-1-fluoro-*myo*-inositol derivative (**11**). Because of the symmetry inherent in the *myo*-inositol molecule, the (+)-isomer of (**11**) is equivalent to 1D-1-deoxy-1-fluoro-*myo*-inositol. This latter compound may be capable of blocking the entire PI cascade should it be able to compete with inositol for phosphatidylinositol synthetase.

Initial biological uptake experiments reveal the ability of (**11**) to substitute for *myo*-inositol. The effects of these inositol isosteres on second messenger signalling processes relevant to cell growth and differentiation will be reported separately.[8,9]



Scheme 3. Synthesis of (−)-1L-1-deoxy-1-fluoro- and (+)-1D-1-deoxy-1-fluoro-*myo*-inositol.

The present work thus provides the first synthesis of a unique fluorine-containing isostere of *myo*-inositol, a substance present universally within plant and animal cells.

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9 Satisfactory spectroscopic and analytical data were obtained for all new compounds reported herein.