An unusual reaction of *myo*-inositol with sulphur tetrafluoride

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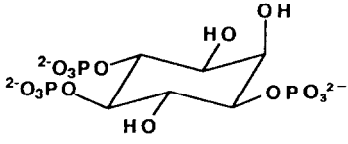
Abstract

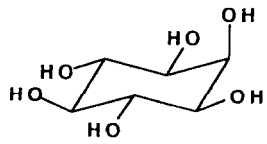
Myo-inositol was treated with a mixture of sulphur tetrafluoride and anhydrous hydrofluoric acid to yield a novel compound, the cyclic sulphite ester of 2β,3β-difluoro-7-oxabicyclo[2,2,1]heptane-5α,6α-diol. The structural assignment and possible mechanism is described.

Introduction

Since the first reports in 1983–4 that the cyclitol polyphosphate, D-*myo*-inositol 1,4,5-trisphosphate (**1**), biosynthetically derived from *myo*-inositol (**2**), acts as a second messenger and is the long-sought-after link between the spatially separated events of receptor stimulation and the mobilization of calcium from intracellular stores [1, 2], interest in this molecule has increased dramatically. Interest arises because second messengers, their receptors as well as enzymes involved in their metabolism are potential targets for rational drug design.



(1)



(2)

Over the last six years many groups have published on the synthesis of inositol polyphosphates [3–5]. More recently researchers have turned their attention to the synthesis of the fluoro analogues of inositol, which have the potential to inhibit or modulate the cell-signalling system. A series of monofluorinated and some *gem*-difluorinated analogues of *myo*-inositol have been reported [6–18]. All the published methods for the preparation of such analogues either involve careful multistep syntheses using a wide variety of

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elegant protecting groups or the use of expensive starting materials. We have been investigating the direct fluorination of unprotected *myo*-inositol and the result of one study is reported here.

Experimental

Melting points are reported uncorrected. ^{1}H and ^{19}F NMR spectra were recorded on a Bruker AM400 instrument using deuterated chloroform as the solvent. Tetramethylsilane was used as an internal standard for the chemical shift downfield in the ^{1}H NMR spectra at 400 MHz. Fluorotrichloromethane was used as external standard for the chemical shift downfield in the ^{19}F NMR spectra at 376.5 MHz. Mass spectra were recorded on a Kratos MS80RF mass spectrometer. Column chromatography was performed with Kieselgel 60, 70–230 mesh ASTM (Merck). Elemental analysis was calculated using a Perkin-Elmer 240 C instrument.

*The cyclic sulphite ester of 2β,3β-difluoro-7-oxabicyclo[2,2,1]heptane-5α,6α-diol (**3**)*

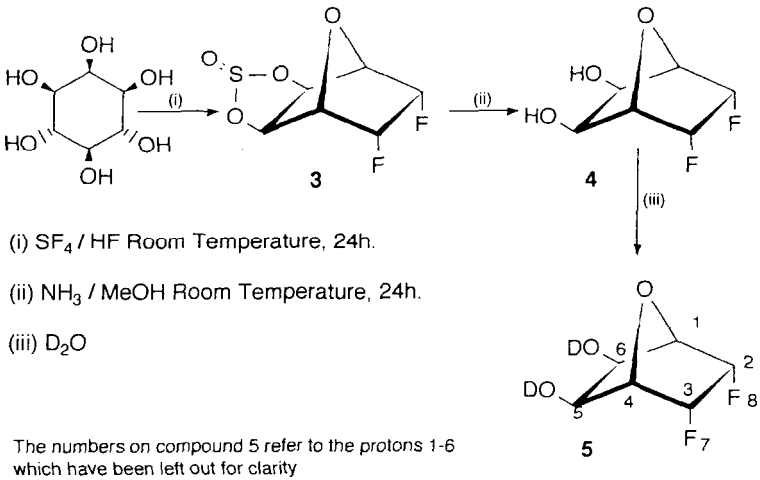
Sulphur tetrafluoride (15 cm^3) and anhydrous hydrofluoric acid (12 cm^3) was added to *myo*-inositol (5.0 g, 27.75 mmol) contained in a stainless-steel bomb cooled to −78 °C. The bomb was sealed, allowed to warm to room temperature and agitated overnight. The bomb was cooled to −78 °C and the contents poured into a polythene beaker and left to stand overnight. A light brown solid was obtained which was dissolved in chloroform (50 cm^3), washed with water (2 × 30 cm^3) dried over $MgSO_4$ and evaporated to afford a pale brown solid. This was recrystallised from hot methanol giving **3** as colourless needles, m.p., 156 °C; yield, 44%. Elemental analysis: Found: C, 34.1; H, 3.0%. $C_6H_6F_2O_2S$ requires: C, 34.0; H, 2.8%. ^{19}F NMR δ: −211 (d, $^{2}J_{HF}$ = 56.3 Hz, 2CHF). ^{1}H NMR δ: 5.37 (t, 3a, 7a); 4.83 (m, 4, 7); 5.1–4.9 (m, 5, 6). MS (NH_3) *m/e*: 213 $(M+1)^+$; 148 $(M-SO_2)$.

*2β,3β-Difluoro-7-oxabicyclo[2,2,1]heptane-5α,6α-diol (**4**)*

A solution of the cyclic sulphite ester (**3**) (1.0 g, 4.7 mmol) and 8 M ammonia/methanol (100 cm^3) was stirred for 24 h at room temperature. The reaction mixture was evaporated to dryness and the residue obtained was dissolved in the minimum amount of methanol and purified by silica gel column chromatography eluting with chloroform/methanol (9:1). Solvents were removed by evaporation to yield a colourless solid which was recrystallised from hot methanol, m.p., 148–150 °C; yield, 38%. Elemental analysis: Found: C, 43.1; H, 4.8%. $C_6H_8F_2O_3$ requires C, 43.4; H, 4.8%. ^{1}H NMR δ: 4.95 (half AA'BB', 8, 9); 4.9–4.7 (m, 2, 3); 4.4 (m, 1, 4); 4.15 (m, 5, 6). MS (NH_3) *m/e*: 167 $(M+1)^+$. The deuterated derivative **5** was prepared by shaking a solution of **4** in $CDCl_3$ with D_2O in a 5 mm NMR tube. ^{1}H NMR δ: 4.9–4.7 (m, 2, 3); 4.4 (m, 1, 4); 4.13 (t, 5, 6; J = 1.81 Hz).

Results and discussion

Myo-inositol was treated with sulphur tetrafluoride and anhydrous hydrofluoric acid at room temperature to yield a colourless crystalline product in 36–44% yield. The product was shown to be a novel compound, the cyclic sulphite ester of 2β,3β-difluoro-7-oxabicyclo[2,2,1]heptane-5α,6α-diol (**3**) (Scheme 1). Increasing the reaction temperature had no effect on either the product obtained nor the yield. The structural assignment of **3** was based on an analysis of its 400 MHz proton spectrum Protons 3a and 7a (Fig. 1) appeared as a lowfield triplet centred at 5.37 ppm, the two −CHF protons, 5 and 6, appeared as a multiplet at 5.1–4.9 ppm and the two bridgehead protons, 4 and 7, appeared as a multiplet at 4.83 ppm. Decoupling the



(i) SF_4 / HF Room Temperature, 24h.

(ii) NH_3 / MeOH Room Temperature, 24h.

(iii) D_2O

The numbers on compound 5 refer to the protons 1-6 which have been left out for clarity

Scheme 1.

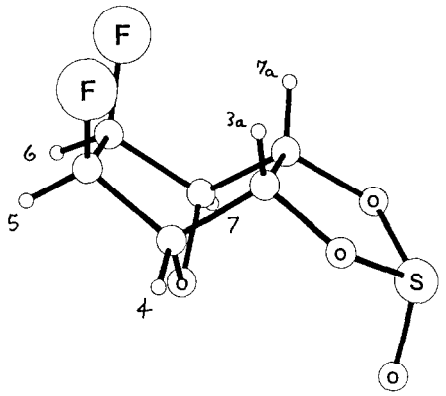


Fig. 1. Structure of the cyclic sulphite ester of 2β,3β-difluoro-7-bicyclo[2,2,1]heptane-5α,6α-diol.

lowfield triplet had no effect on the spectrum indicating that the multiplicity is due to fluorine only. In bicycloheptane derivatives, zero coupling is normally observed between *endo*-protons and bridgehead protons since the dihedral angle is close to 90°. Consequently, it is reasonable to suggest that the cyclic sulphite group is *exo*. This is substantiated by the fact that protons 3a and 7a are coupled to fluorine only, suggesting a through-space contribution with the fluorine atoms *endo* as shown in **3**. Further evidence was obtained from NOE experiments in which irradiation of protons 3a and 7a caused a corresponding enhancement in the fluorine spectrum.

Removal of the cyclic sulphite group was brought about by using ammonia in methanol to give the dihydroxy compound **4** (Scheme 1). The structural assignment of **4** was based on an analysis of its 400 MHz proton NMR spectrum. The two hydroxy protons appeared as half of an AA'BB' pattern centred at 4.95 ppm, and the two −CHF protons, 2 and 3, appeared as a symmetrical multiplet at 4.9–4.7 ppm. Protons 5 and 6 appeared as a high-field multiplet at 4.15 ppm.

Exchanging the two hydroxy groups with D_2O (compound **5**) caused collapse of this multiplet to a triplet. The bridgehead protons 1 and 4 appeared as a multiplet centred at 4.4 ppm. Decoupling the latter multiplet reduced protons 2 and 3 to appear as half of an AA'XX' pattern. This was analysed using the Bruker PANIC program to give the coupling constants and calculated spectrum. The parameters from the calculated spectrum were used with approximate values for the other couplings to calculate the entire spectrum for the deuterium-exchanged product. The results showed a reasonable fit, although a full iterative analysis was not attempted at this time*. X-Ray diffraction analysis of compound **3** confirmed the NMR structural assignment (Fig. 1).

A proposed mechanism describing the formation of **3** is given in Scheme 2. In the first step, sulphur tetrafluoride reacts with the C-1 hydroxy to form the alkoxysulphur trifluoride intermediate **6**. For steric reasons, the reaction is preferred for equatorial hydroxy groups, whereas reaction at the axial C-2 hydroxy would lead to unfavourable 1,3-diaxial interactions with the intermediate and the axial hydrogens at C-4 and C-6. It is important to note that the formation of the alkoxysulphur trifluoride intermediate at the C-4, C-5 and C-6 hydroxy groups does not give the observed product if the proposed mechanism is followed through. The reason for this specificity is not known. The oxygen lone pair on the axial hydroxy then attacks sulphur with concomitant elimination of hydrogen fluoride to form the five-membered cyclic sulphite system **7**. Sulphur tetrafluoride reacts again at the C-6 hydroxy. If reaction were to occur at the C-3 hydroxy and the mechanism followed through, the incorrect isomer would be obtained; again there is no explanation for this specificity.

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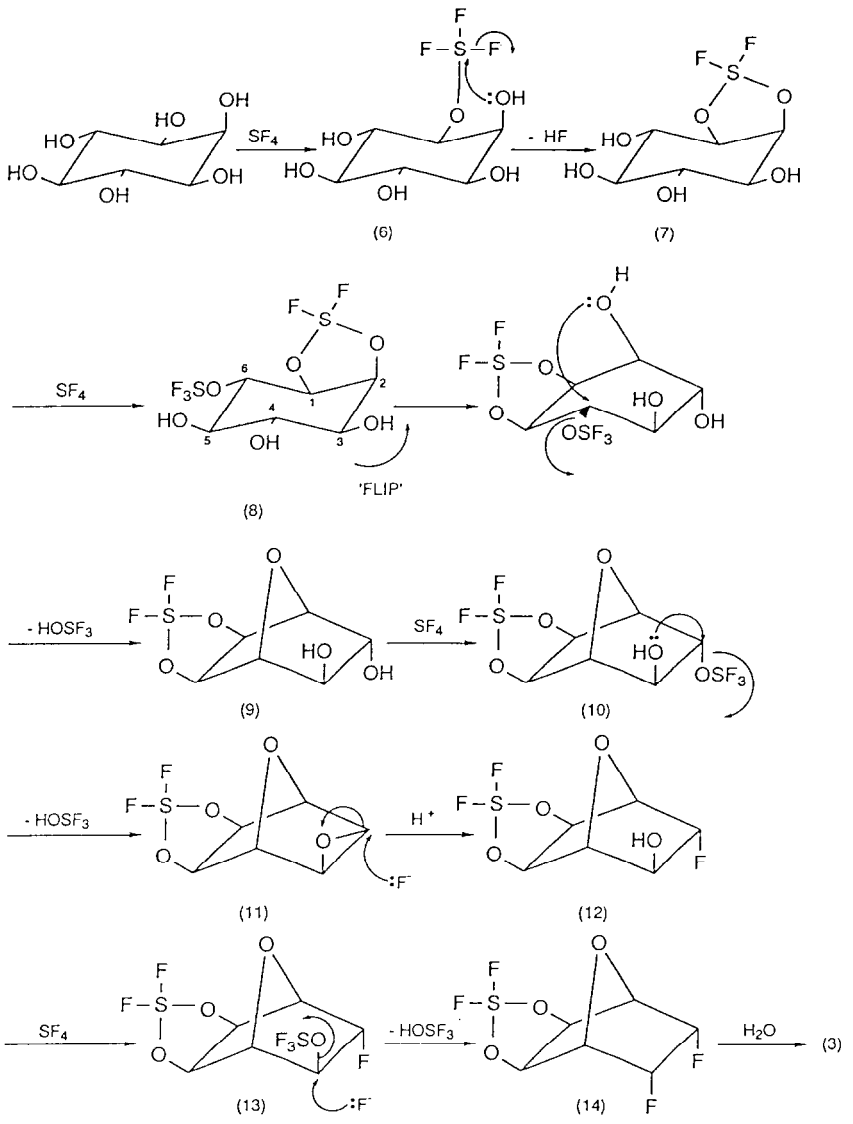
*When complete, a full analysis of compound **5** and of related compounds will be reported. Approximate values ($CDCl_3$): $J_{1,2}=5.4$, $J_{2,3}=7.5$; $J_{3,4}=5.4$; $J_{5,6}=6.2$; $J_{1,7}\sim 0$; $J_{2,7}=53.5$; $J_{2,8}=4.3$; $J_{6,7}=2.1$; $J_{6,8}=1.3$ Hz.



Scheme 2.

The alkoxysulphur trifluoride intermediate **8** flips to the boat conformation, which might be expected to be energetically preferred since the five-membered cyclic sulphite system 'flattens' the cyclohexane ring. The 1,4-epoxy bridge is formed via intramolecular S_N2 displacement of OSF_3^- by the lone pair on the C-3 hydroxy to give **9**. Sulphur tetrafluoride attacks the *endo*-hydroxy of **9** to give intermediate **10**. Intramolecular S_N2 displacement of OSF_3^- by the lone pair on the *exo*-hydroxy gives the *exo*-epoxide intermediate **11**. Epoxide opening by the fluoride ion gives the fluorinated intermediate **12**.

Sulphur tetrafluoride now attacks the *exo*-hydroxy giving intermediate **13** which undergoes intermolecular S_N2 displacement by the fluoride ion to give **14**; aqueous work-up gives the final product **3**. Considering once again the epoxide-forming steps, on steric grounds attack by sulphur tetrafluoride on the *exo*-hydroxy would be expected to be the most favoured. However, this would give the *endo*-epoxide and hence the *exo*-1,2-difluoride as the product. Again the reasons for this apparent specificity are unclear.

Acknowledgements

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