Synthesis of Phenyl [(*R*)^{16}O,^{17}O,^{18}O]Sulphate and the Stereochemical Course of a Sulphuryl Transfer Reaction

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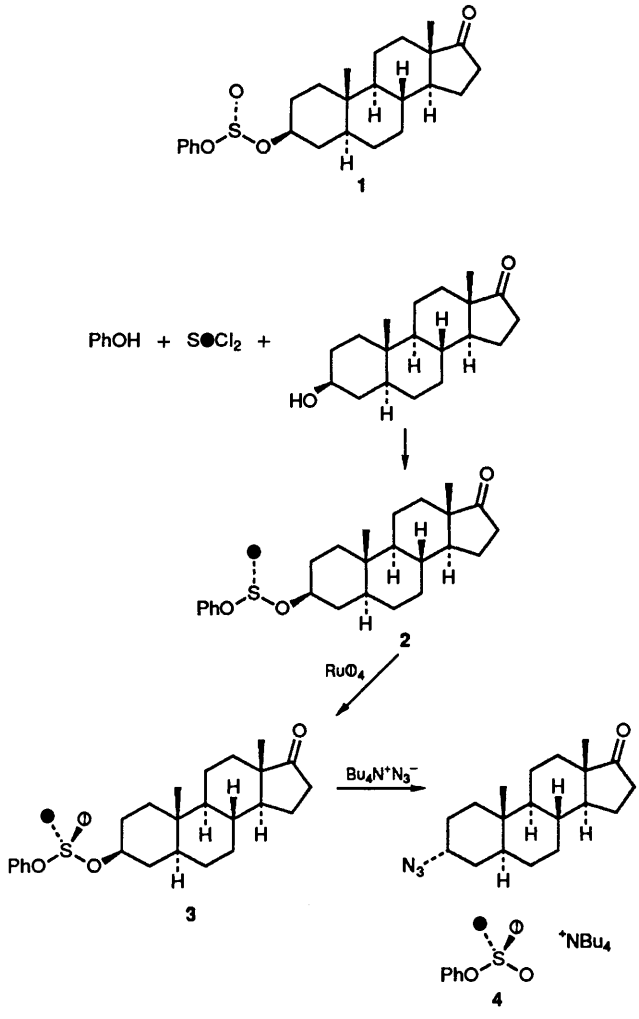
Phenyl [(*R*)^{16}O,^{17}O,^{18}O]sulphate is synthesised and the stereochemical course of sulphuryl transfer to a secondary alcohol shown to proceed with inversion of configuration at sulphur.

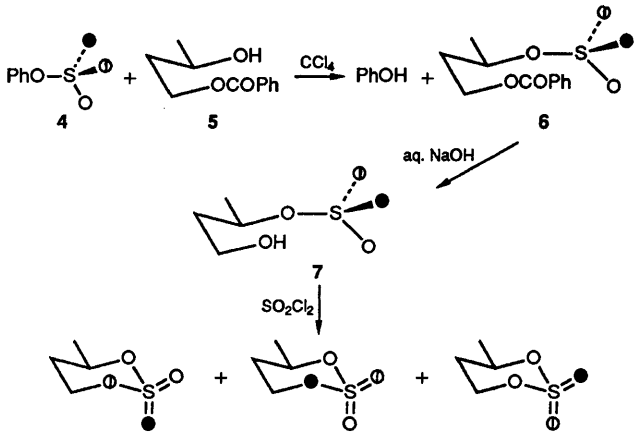
In order to study the stereochemical course of chemical and enzyme catalysed sulphuryl transfer reactions, a general strategy for the synthesis of chiral [^{16}O,^{17}O,^{18}O]sulphate monoesters has been developed.[1,2] A chirally labelled aryl sulphate was now required to further these investigations. A preliminary search for a chiral alcohol that would form a crystalline sulphite diester with phenol and thionyl chloride, and would not be susceptible to oxidation by ruthenium tetroxide led us to select 3β-cholestanol and epiandrosterone. Both of these steroidal alcohols form phenyl sterol sulphite diesters when one molar equivalent of phenol and 3β-cholestanol or epiandrosterone is reacted successively with thionyl chloride in the presence of pyridine. A single diastereoisomer of phenyl epiandrosterone sulphite diester crystallised readily and is shown to have the (R_S)-configuration **1**, by X-ray crystal structure analysis.[3] With this knowledge phenyl [(*R*)^{16}O,^{17}O,^{18}O]sulphate was synthesised by the route outlined in Scheme 1.

[^{18}O]Thionyl chloride was prepared from sulphur [$^{18}O_2$]dioxide (99 atom% ^{18}O) and 1,4-bis(trichloromethyl)-benzene in the presence of a catalytic amount of iron(III) chloride in a sealed tube at 20 °C for 3 days: the [^{18}O]thionyl chloride (83%) was purified by fractional distillation.[4] One equivalent of phenol in benzene solution was added slowly to a stirred solution of the [^{18}O]thionyl chloride in benzene in the presence of pyridine and this was allowed to react for 1 h. Epiandrosterone (1 equiv.) in benzene solution was then added and the reaction mixture stirred for 15 min. The [^{18}O]sulphite diester **2** was obtained (43%) after flash chromatography on silica gel,[5] and was recrystallised from ether–hexane prior to oxidation. The [^{18}O]sulphite diester **2** was oxidised to the corresponding [^{17}O,^{18}O]sulphate diester **3** using a modification of our previously described method for the oxidation of sulphites to labelled sulphates.[6] The [^{18}O]sulphite **2** is an aryl sulphite diester, unlike the previously studied sulphites diesters,[1,2,6] and is not stable under the aqueous conditions of the catalytic oxidation method.[6] Ruthenium tetroxide was prepared, therefore, from ruthenium dioxide dihydrate (200 mg, 1.18 mmol) and sodium metaperiodate (600 mg, 2.8 mmol) in a vigorously stirred, biphasic system consisting of CCl_4 (25 ml) and water (5 ml); the organic layer containing the ruthenium tetroxide was dried (over Na_2SO_4) and [^{17}O]water (45.0% ^{17}O, 20.2% ^{16}O, 34.8% ^{18}O, 0.5 ml) containing anhydrous Na_2HPO_4 (10 mg) added and isotope exchange allowed to occur by vigorously stirring the mixture for 24 h.† The ruthenium [$^{17}O_4$]tetroxide solution was dried and used (in a slightly greater than stoichiometric amount) to oxidise the [^{18}O]sulphite diester **2** at 0 °C (reaction time 10 min) to phenyl epiandrosterone [^{17}O,^{18}O]sulphate **3** in 76% yield.

Having previously established the configuration at sulphur of the unlabelled sulphite diester **1** and knowing that the oxidation of sulphites to sulphates with ruthenium tetroxide



Scheme 1 Synthesis of phenyl [(*R*)^{16}O,^{17}O,^{18}O]sulphate. Φ = ^{17}O; ● = ^{18}O.



Scheme 2 The stereochemical course of a sulphuryl transfer reaction. The product **6**, after debenzoylation and cyclization was analysed by FTIR spectroscopy (see Fig. 1). Φ = ^{17}O; ● = ^{18}O.

† Basic conditions have been found to catalyse the exchange of oxygen isotopes into RuO_4. Preliminary studies were performed under similar conditions using 99% [^{18}O]H_2O. The resulting ruthenium [$^{18}O_4$]tetroxide reacted with racemic *cis*-4-methyl-2-oxo-1,3,2-dioxathiane to give the corresponding 4-methyl-2,2-[^{18}O]dioxo-1,3,2-dioxathiane in very high enrichment (by FTIR), indicating that isotope exchange had reached equilibrium.

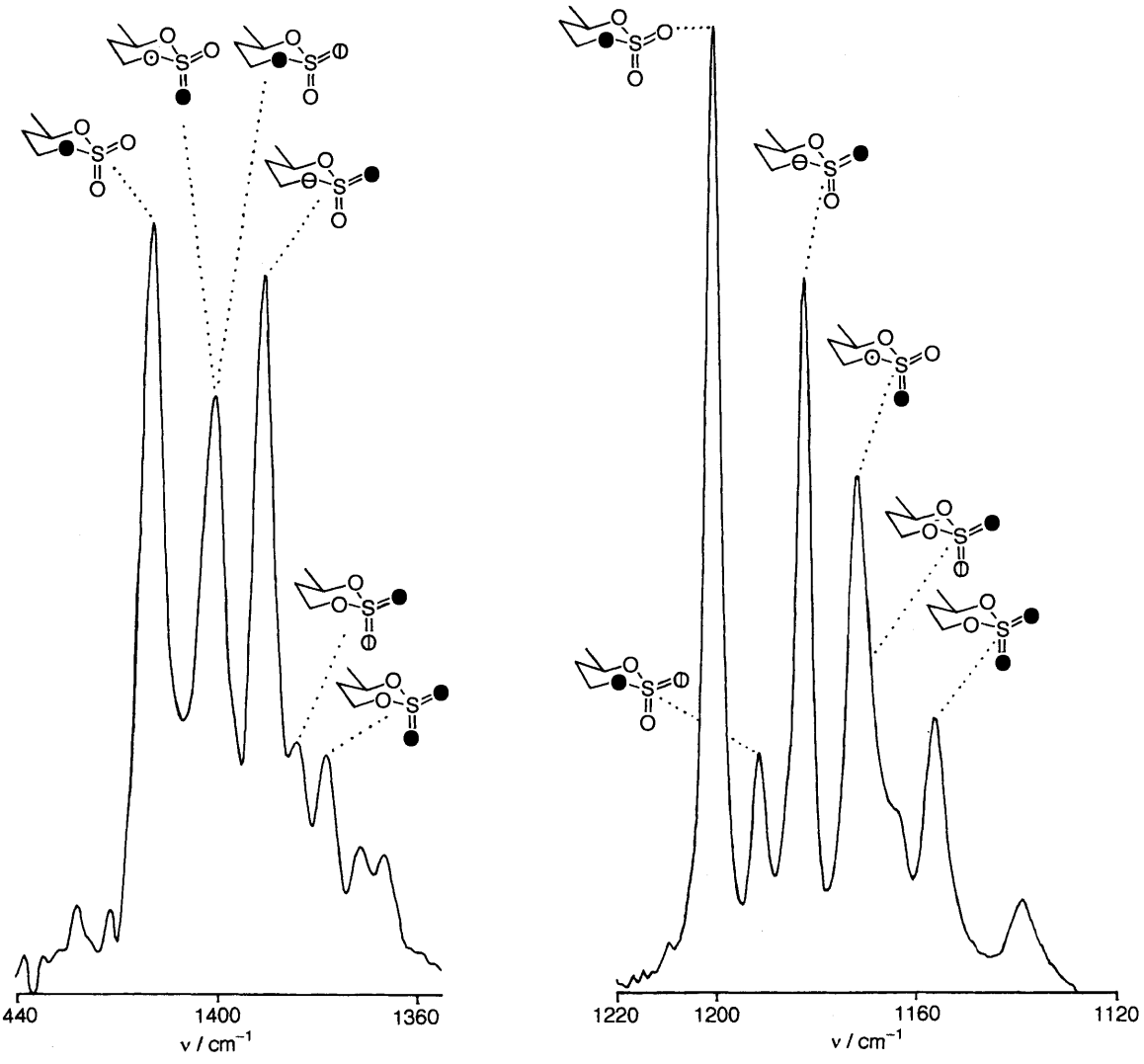


Fig. 1 The FTIR spectrum showing the antisymmetric (1414–1378 cm^{-1}) and symmetric (1201–1157 cm^{-1}) $>SO_2$ stretching frequencies of the mixture of isotopomers derived by cyclizing (1*R*)-3-hydroxy-1-methylpropyl [^{16}O,^{17}O,^{18}O]sulphate **7** with sulphuryl chloride. The resolution was enhanced by Fourier deconvolution; for the antisymmetric stretching region a linewidth of 20 cm^{-1} and an enhancement factor of 2.0 was used, whereas for the symmetric stretching region a linewidth of 10 cm^{-1} and an enhancement factor of 1.5 was used. Isotopes in a bridging position do not influence the $> SO_2$ stretching frequencies.[2] ⦶ = ^{17}O; ● = ^{18}O; ⊖ = ^{17}O and ^{18}O; ⊙ = ^{16}O, ^{17}O and ^{18}O.

occurs with retention of configuration,[6] the [^{17}O,^{18}O]sulphate diester **3** must have the (R_S)-configuration as shown. Phenyl epiandrosterone [(*R*)^{17}O,^{18}O]sulphate diester **3** on treatment with tetrabutylammonium azide[7] in CH_2Cl_2 at room temperature for 18 h was converted to phenyl [(*R*)^{16}O,^{17}O,^{18}O]sulphate tetrabutylammonium salt **4** in 45% yield after purification on Sephadex G-10.

Phenyl [(*R*)^{16}O,^{17}O,^{18}O]sulphate tetrabutylammonium salt **4** was incubated with (1*R*)-3-benzoyloxy-1-methylpropan-1-ol **5**,[8] in carbon tetrachloride at 100 °C for 16 h (in a reacti-vial) by which time sulphuryl transfer was essentially complete. The (1*R*)-3-benzoyloxy-1-methylpropyl [^{16}O,^{17}O,^{18}O]sulphate **6** was debenzoylated with aqueous sodium hydroxide solution and the (1*R*)-3-hydroxy-1-methylpropyl [^{16}O,^{17}O,^{18}O]sulphate **7** as its pyridinium salt cyclized with sulphuryl chloride.[2] The mixture of isotopomers so generated was investigated by FTIR; the spectrum of the symmetric and antisymmetric stretching frequences are shown in Fig. 1. The distribution of isotopomers is that expected from the S_S enantiomer of (1*R*)-3-hydroxy-1-methylpropyl [^{16}O,^{17}O,^{18}O]sulphate,[2]‡ indicating that the sulphuryl transfer reaction has proceeded with inversion of configuration at sulphur.

Phenyl [^{16}O,^{17}O,^{18}O]sulphate was also prepared by way of the crystalline diastereoisomer of phenyl 3β-cholestanol [^{18}O]sulphite. Although an X-ray crystallographic structural analysis of the unlabelled phenyl 3β-cholestanol sulphite was not performed, the phenyl [^{16}O,^{17}O,^{18}O]sulphate was shown to have the same configuration as the phenyl [(*R*)^{16}O,^{17}O,^{18}O]sulphate obtained from phenyl epiandrosterone [^{17}O,^{18}O]sulphate **3**, by transfer of the labelled sulphuryl group to (1*R*)-3-benzoyloxy-1-methylpropan-1-ol (*vide supra*), followed by alkaline hydrolysis, cyclization with

‡ The '^{17}O-water' used for the preparation of the ruthenium [$^{17}O_4$]tetroxide contained 45% ^{17}O, 20.2% ^{16}O and 34.8% ^{18}O so where sites are shown as ^{17}O it should be realised that a fraction of those sites will contain ^{16}O and ^{18}O.

sulphuryl chloride and FTIR analysis.[2] Hence the phenyl 3β-cholestanol sulphite must also have the (R_S)-configuration.

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