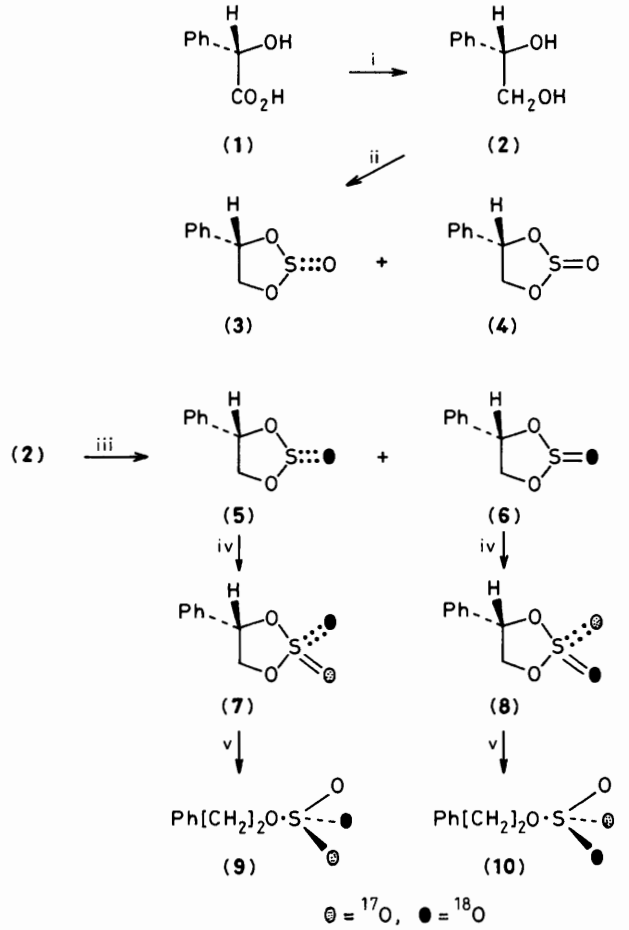
Enantiomeric Chiral [^{16}O,^{17}O,^{18}O]Sulphate Esters

Gordon Lowe* and Salvatore J. Salamone

The Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY, U.K.

A general strategy has been developed for the synthesis of chiral [^{16}O,^{17}O,^{18}O]sulphate esters which is illustrated by the synthesis of the enantiomers of 2-phenylethyl [^{16}O,^{17}O,^{18}O]sulphate.

Stereochemical analysis has long been recognised as a powerful method for elucidating the mechanisms of chemical and enzyme-catalysed reactions. When the reaction in question occurs at a *pro-* or *pro-pro*-chiral centre, that centre must be made chiral, ideally by isotopic substitution. Hitherto only two *pro-pro*-chiral centres have been made chiral by isotopic substitution, namely methyl groups using ^{1}H, ^{2}H, and ^{3}H,[1] and phosphate monoesters or anhydrides using ^{16}O, ^{17}O, and ^{18}O.[2] With a view to investigating the stereochemical course of chemical and enzyme-catalysed reactions of sulphate monoesters we have developed a general strategy for the synthesis of chiral [^{16}O,^{17}O,^{18}O]sulphate esters.



Scheme 1. The synthesis of 2-phenylethyl (*S*)-[^{16}O,^{17}O,^{18}O]sulphate (**9**) and 2-phenylethyl (*R*)-[^{16}O,^{17}O,^{18}O]sulphate (**10**). *Reagents:* i, $LiAlH_4$; ii, $SOCl_2$; iii, $S^{18}OCl_2$; iv, RuO_2, $NaIO_4$, $H_2{}^{17}O$; v, $Bu^n{}_4N^+BH_4^-$.

(*S*)-Mandelic acid (**1**) was reduced by lithium aluminium hydride to 2(*S*)-phenylethane-1,2-diol (**2**),[3] which on treatment with thionyl chloride gave the *cis*- and *trans*-2-oxo-4(*S*)-phenyl-1,3,2-dioxathiolanes (**3**) and (**4**). Although their configurations could be assigned from spectroscopic evidence,[4] they were rigorously established by an *X*-ray crystallographic analysis of the *trans*-isomer.[5] [^{18}O]Thionyl chloride was prepared from sulphur [$^{18}O_2$]dioxide (99 atom % ^{18}O) and phosphorus pentachloride and purified by fractional distillation. Reaction of [^{18}O]thionyl chloride with 2(*S*)-phenylethane-1,2-diol gave *cis*-2-[^{18}O]oxo-4-(*S*)-phenyl-1,3,2-dioxathiolane (**5**) and *trans*-2-[^{18}O]oxo-4(*S*)-phenyl-1,3,2-dioxathiolane (**6**) which were separated chromatographically. Their i.r. spectra had ν_{max} (CCl_4) (S=^{18}O) 1173 and 1177 cm^{-1} respectively whereas the unlabelled *cis*- and *trans*-diastereoisomers had ν_{max} (CCl_4) (S=^{16}O) 1215 and 1222 cm^{-1} respectively. Oxidation of the separated diastereoisomers (**5**) and (**6**) with ruthenium [^{17}O]tetroxide generated *in situ* from ruthenium(IV) oxide, sodium periodate, and [^{17}O]water (52.8 atom % ^{17}O, 9.4 atom % ^{16}O, 37.8 atom % ^{18}O) in the presence of (ethanol free) chloroform, gave the diastereotopic 2(*R*)-[^{17}O,^{18}O]- and 2(*S*)-[^{17}O,^{18}O]-dioxa-4(*S*)-phenyl-1,3,2-dioxathiolanes, (**7**) and (**8**) respectively; we have established that the oxidation with ruthenium tetroxide occurs with retention of configuration at sulphur.[6] Finally, reductive cleavage of the benzylic oxygen bond was achieved with tetrabutylammonium borohydride in dimethylformamide. Since this occurs without perturbing any of the sulphur to oxygen bonds the absolute configuration of the chiral [^{16}O,^{17}O,^{18}O]sulphate esters follows from the method of synthesis and the absolute configuration of (*S*)-mandelic acid. Thus, 2(*R*)-[^{17}O,^{18}O]dioxa-4(*S*)-phenyl-1,3,2-dioxathiolane (**7**) gives 2-phenylethyl (*S*)-[^{16}O,^{17}O,^{18}O]sulphate (**9**) and 2(*S*)-[^{17}O,^{18}O]dioxa-4-(*S*)-phenyl-1,3,2-dioxathiolane (**8**) gives 2-phenylethyl (*R*)-[^{16}O,^{17}O,^{18}O]sulphate (**10**) which were isolated as their crystalline tetrabutylammonium salts. Their chiroptical properties are currently being investigated.

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