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Homochiral 2,3-Epoxy Sulfides as precursors to E-γ-Hydroxy-α,β-Unsaturated Sulfoxides and Sulfones.

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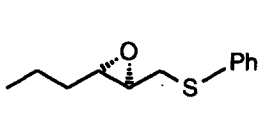
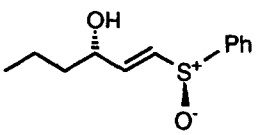
Abstract: The synthesis of E-γ-hydroxy-α,β-unsaturated sulfoxides and sulfones from the corresponding homochiral 2,3-epoxy sulfides is described with excellent control of double bond geometry and stereochemistry at both the sulfoxide and secondary alcohol chiral centres.

Optically pure α,β-unsaturated sulfoxides are of considerable current interest as chiral dienophiles[1,2], dipolarophiles[3] and Michael acceptors[4] primarily because of the potential of the sulfoxide moiety as a stereocontrolling element. The corresponding α,β-unsaturated sulfones are also the subject of recent attention and can undergo analogous reactions but without the potential for stereocontrol in unsubstituted systems[5]. In the case of unsaturated sulfones, γ-substitution has been shown to have a strong influence on the facial selectivity for addition to the carbon-carbon double bond.[6] However the corresponding γ-hydroxy-α,β-unsaturated sulfoxides have been relatively little investigated and are intriguing substrates for stereochemical studies due to the presence of two potential controlling elements, the sulfoxide and alcohol (or its equivalent).[7] In this communication we present new, versatile routes to γ-hydroxy-α,β-unsaturated sulfoxides (2,3) and sulfone (4) with excellent stereocontrol starting from the homochiral 2,3-epoxy sulfide (1).[8]



(1)



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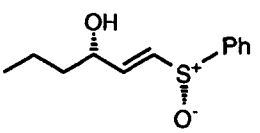

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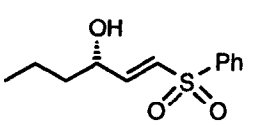


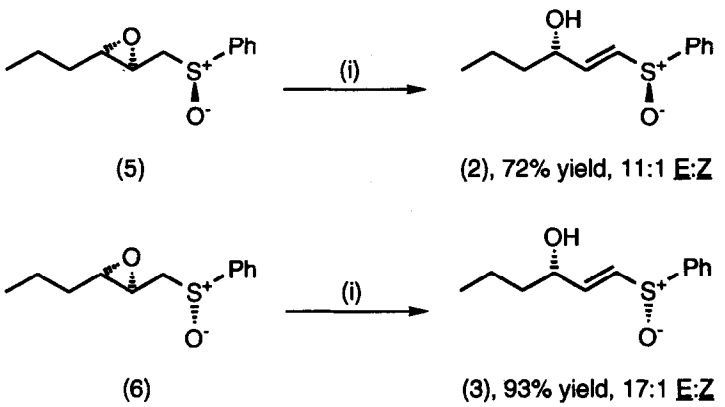
(4)

We have recently reported methods for the stereoselective synthesis of 2,3-epoxy sulfoxides[9] using a double enantioselective oxidation approach,[10] exploiting the known enantioselectivity of the Sharpless asymmetric epoxidation[11] and also the complementary asymmetric sulfur oxidation methods of Kagan[12] and Davis[13]. We have also reported that under Lewis acidic conditions, 2,3-epoxy sulfoxides undergo regiospecific hydrolysis at C-3 *via* novel cyclic sulfoxonium salts.[8a]

We now wish to report processes for the preparation of homochiral E-γ-hydroxy-α,β-unsaturated sulfoxides either from diastereomerically pure 2,3-epoxy sulfoxides by base catalysed elimination, or from diastereomeric mixtures, *via* a novel kinetic resolution process involving formation of a cyclic sulfonium salt intermediate.

The diastereomerically pure 2,3-epoxy sulfoxides (5) and (6) are available by asymmetric oxidation of the

homochiral 2,3-epoxy sulfide (1) (up to 13:1 selectivity) followed by removal of the minor diastereomer by column chromatography.[10] Simple treatment of (5) and (6) with aqueous sodium hydroxide efficiently converts them to the corresponding E-γ-hydroxy-α,β-unsaturated sulfoxides (2) and (3)[14] in good yield (scheme 1). Two important points should be noted. Firstly, the stereochemical integrity of the 2,3-epoxy sulfoxide substrate is retained, and secondly, high selectivity for formation of the E-geometry at the new double bond is observed (≥11:1). This is in contrast to recent observations for elimination of 2,3-epoxy sulfides, where significant amounts of the Z-isomers are formed (up to 1.7:1 E/Z).[8c,d]



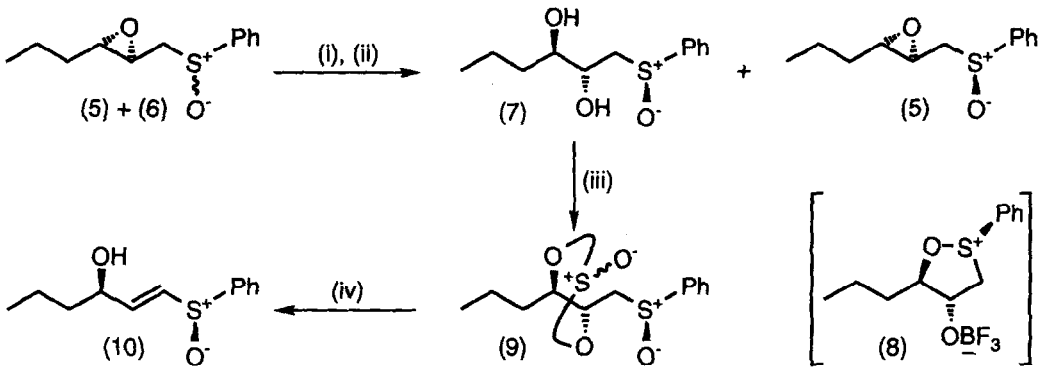
Reagents: i, NaOH, H_2O, room temperature.

Scheme 1.

Although this process is generally satisfactory, removal of the minor diastereomer of the 2,3-epoxy sulfoxide (5) or (6) by column chromatography was a problem, particularly on a large scale. We therefore decided to investigate other routes to these systems.

We had previously noted that for the two diastereomeric 2,3-epoxy sulfoxides (5) and (6), a considerable difference in rate existed for the formation of cyclic sulfoxonium salts by $BF_3.OEt_2$ catalysed intramolecular epoxide ring opening by the sulfoxide oxygen.[8a] We were therefore particularly interested in whether such a rate difference could be exploited in a kinetic resolution process, where a mixture of (5) and (6), prepared by non-selective oxidation, could be reacted under conditions such that only one diastereoisomer was converted into the sulfoxonium salt (8), whereas the other remained unaffected, and could be isolated at the end of the reaction in a diastereomerically enriched form.

This was indeed the case (scheme 2). After considerable experimentation, the following procedure gave optimum results. $BF_3.OEt_2$ (0.67ml, 5.48mmol) was added to an ether solution of a 1:1 mixture of (5) and (6) (1.02g, 4.57mmol) at -78°C, and the reaction allowed to warm to -9°C. After 50min. at this temperature, aqueous sodium bicarbonate was added which hydrolysed the sulfoxonium salt intermediate (8) to the 2,3-dihydroxy sulfoxide (7) which could be isolated after extraction and recrystallisation (0.454g, 1.87mmol, 41% yield, >95% d.e.) along with unreacted, resolved 2,3-epoxy sulfoxide (5) (0.451g, 2.01mmol, 44% yield, 91% d.e.). Importantly, no column chromatography was necessary as (7) recrystallises readily from benzene whereas (5) remains in solution. At higher temperatures and/or prolonged reaction times, (5) could be isolated in >95% d.e., although yields and the diastereomeric purity of (7) were lower. The resolved 2,3-epoxy sulfoxide (5) could then be easily converted into the E-γ-hydroxy-α,β-unsaturated sulfoxide (2) by treatment with aqueous base as described above (scheme 1).

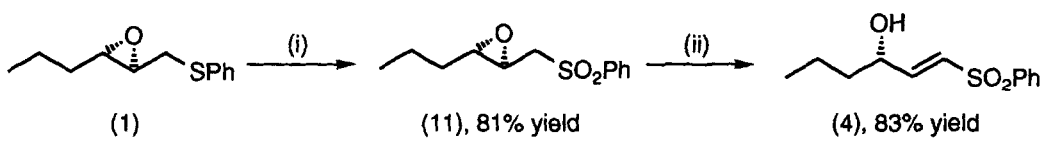


Reagents: i, $BF_3.OEt_2$, Et_2O, -78→-9°C, 50 min.; ii, $NaHCO_3$ (aq.); iii, $SOCl_2$, NEt_3, CH_2Cl_2; iv, DBU (3 eq.), CH_2Cl_2, r.t., 4h.

Scheme 2.

We also wished to convert the 2,3-dihydroxy sulfoxide (7) into the corresponding γ-hydroxy-α,β-unsaturated sulfoxide. Fortunately, we were able to adapt procedures previously used for the synthesis of γ-hydroxy-α,β-unsaturated nitriles, sulfones and amides[15] from the corresponding dihydroxy precursors *via* intermediate sulfites, to carry out this transformation. Thus treatment of (7) with thionyl chloride and triethylamine formed the intermediate sulfite (9) as a mixture of diastereoisomers, which could be readily eliminated with DBU to give exclusively the E-γ-hydroxy-α,β-unsaturated sulfoxide (10) in 89% overall yield.

Synthesis of γ-hydroxy-α,β-unsaturated sulfones can also be readily carried out from homochiral 2,3-epoxy sulfides using similar methodology (scheme 3).[16] Thus oxidation of (1) to the corresponding sulfone using an excess of *meta*-chloroperoxy benzoic acid (*m*-CPBA) gives the sulfone (11), which undergoes facile β-elimination when treated with DBU, resulting in formation of the homochiral E-γ-hydroxy-α,β-unsaturated sulfone (4) in excellent overall yield.[17]



Reagents: i, m-CPBA (2.5 eq.), CH_2Cl_2; ii, DBU, CH_2Cl_2.

Scheme 3.

In conclusion, we have shown how homochiral, oxidised 2,3-epoxy sulfide derivatives can be used as precursors to γ-hydroxy-α,β-unsaturated sulfoxides and sulfones using a number of different approaches which allow full control of stereochemistry and double bond geometry, and are practical for large scale work. We now have access to all four diastereoisomers of the γ-hydroxy-α,β-unsaturated sulfoxides, and further investigations into their chemistry are currently underway.[18]

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14.The stereochemical assignments and ^{1}H NMR data for the 2,3-epoxy phenylsulfoxides (5) and (6)) have been discussed previously in reference 8a. ^{1}H NMR (300 MHz, C_6D_6); (2), δ0.76 (3H, t, J 6.9 Hz, CH_3CH_2), 1.16-1.38 (4H, m, CH_2CH_2), 2.47 (1H, m, HO-CH-3), 3.95 (1H, m, CH-3), 6.42 (1H, d, J 14.9 Hz, CH-1), 6.58 (1H, dd, J 14.9, 3.8 Hz, CH-2), 6.90-7.01 (3H, m, ArH), 7.48 (2H, d, J 7.6 Hz, ArH); (3) δ 0.71 (3H, t, J 6.8 Hz, CH_3CH_2), 1.06-1.19 (4H, m, CH_2CH_2), 3.76-3.79 (1H, m, CH-3), 6.26 (1H, d, J 14.9 Hz, CH-1), 6.53 (1H, dd, J 14.9, 4.4 Hz, CH-2), 6.98-7.10 (3H, m, ArH), 7.49 (2H, d, J 7.0 Hz, ArH).

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17.^{1}H NMR ($CDCl_3$, 300MHz); (4), δ0.94 (3H, t, J 7.0Hz, CH_3CH_2), 1.40-1.62 (4H, m, CH_2CH_2), 1.82 (1H, s, HO-CH-3), 4.40 (1H, m, CH-3), 6.60 (1H, dd, J 15.0, 2.0Hz, CH-1), 7.00 (1H, dd, J 15.0, 6.5Hz, CH-2), 7.58 (3H, m, ArH), 7.89 (2H, dd, J 7.2, 2.0Hz, ArH).

18.All new compounds were characterised by ^{1}H and ^{13}C NMR, IR, MS, elemental analysis and/or accurate MS.

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