Oxidation of methyl *p*-tolyl sulfide with bakers' yeast: preparation of a synthon of the mevinic acid-type hypocholestemic agents

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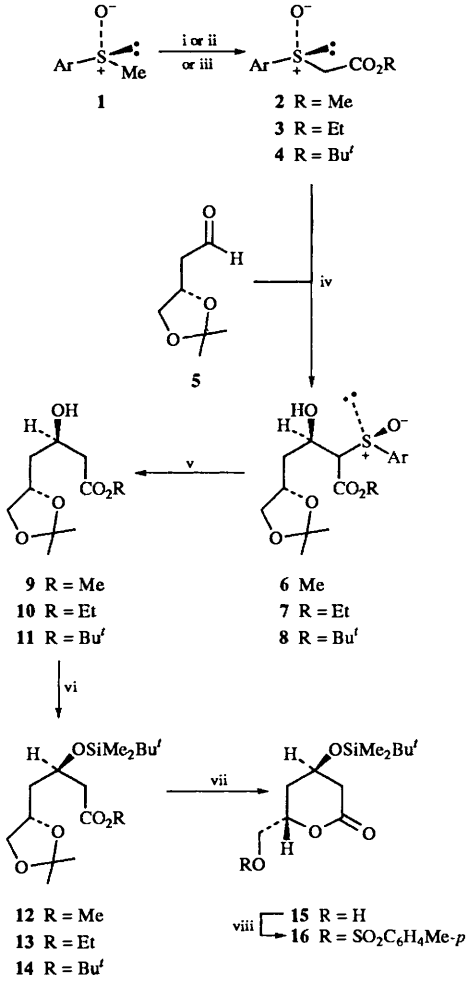
Bakers' yeast oxidized methyl *p*-tolyl sulfide to produce the *R*-sulfoxide **1** in good yield and high enantiomeric excess; the sulfoxide **1** was used to prepare (4*R*,6*S*)-*tert*-butyldimethylsilyloxy-6-hydroxymethyltetrahydropyran-2-one **15**.

Optically active sulfoxides which have an important niche in synthetic organic chemistry[1] can be prepared chemically by oxidation of the corresponding sulfides under Sharpless–Kagan conditions.[2]

However, there have been considerable efforts to find biocatalysts which will also effect stereoselective oxidation of sulfides. Whole cell systems such as the fungi *Aspergillus niger*,[3] *Mortierella isabellina*,[4] *Helminthosporium* sp[5] and the bacterium *Rhodococcus equi*[6] have been employed. Isolated enzymes such as rat liver cytochrome P_{450} monooxygenase,[7] pig liver FAD-dependent monooxygenase,[8] monooxygenases from *Pseudomonas* sp,[9] the cyclohexanone monooxygenase from *Acinetobacter calcoaceticus*[10] and the chloroperoxidase from *Caldaromyces fumago*[11] have been recommended for the biotransformation of sulfide to sulfoxide.

Since none of the above biocatalysts are readily available, we were interested in exploring the possibility of employing a biocatalyst that would be more useful to the synthetic organic chemist. There are isolated reports that bakers' yeast (*Saccharomyces cerevisiae*) can be used to oxidize sulfides. Thus, 1-(phenylsulfinyl)heptan-2-one has been reported to give racemic sulfoxide (5% yield);[12] 9-thiastearate[13] and methyl styryl sulfide[14] are also oxidized to the sulfoxide with yeast. We have found that methyl tolyl sulfide is oxidized to the crystalline *R*-sulfoxide **1** with good selectivity (92% ee) † using *S. cerevisiae*. The protocol is simple and easy to carry out by a non-expert (*vide infra*).

We have employed the sulfoxide **1** in a novel synthesis of a synthon *en route* to the hypocholestemic agents related to mevinic acid (Scheme 1).[15] The sulfoxide **1** is easily converted into the esters **2**–**4**, the deprotonation of which and subsequent coupling to the aldehyde **5**[16] gave the alcohols **6**–**8**, respectively, with high selectivity. In accord with previous arguments[17] we believe that the C-2(*R*), C-3(*R*) diastereoisomer is the major product formed, from the low-energy transition state **A** shown in Fig. 1. Smaller amounts of the C-2(*R*), C-3(*S*) and C-2(*S*), C-3(*S*) diastereoisomers would be expected to be formed through transition states **B** and **C**, respectively. However, the product distribution could not be investigated in detail owing to the instability of the hydroxy sulfoxides. Desulfurization of the sulfoxides **6**–**8** had to be carried out without delay whereupon the alcohols **9**–**11** were obtained in good yields. A small amount (≤20%) of the C-4 epimers was obtained in each of the crude products as judged by NMR spectroscopy. These products are derived from reaction pathways **B** and **C** in Fig. 1. Silylation of the secondary alcohol group in compounds **9**–**11** furnished the ethers **12**–**14**, respectively. The ethyl ester **13** cyclized to form the δ-lactone **15** on treatment with hot acetic acid in accord with previous work.[16] The *tert*-butyl ester **14** did not cyclize under these reaction conditions and, more surprisingly, the methyl ester gave the lactone **15** only in poor yield. The lactone **15** ($[\alpha]_D$ −7.5, *c* 1.0, $CHCl_3$) was isolated as a crystalline solid and the relative configuration of the substituents at C-4 and C-6 was established by nOe experiments (Fig. 2). Note that the minor C-3(*S*) diastereoisomers observed after step (iv) were



Scheme 1 *Reagents and conditions:* i, LDA, $ClCO_2CH_3$, THF, N_2, −78 °C (81%); ii, LDA, $ClCO_2Et$, THF, N_2, −78 °C (91%); iii, HMDS, BuLi, $[Bu^tCO_2C]_2O$, THF, N_2, −78 °C (62%); iv, Bu^tMgCl, THF, N_2, −78 °C (50–60%); v, Al/Hg, THF, H_2O (10:1) (50–60%); vi, TBDMSCl, imidazole, DMF, N_2, 50 °C, 2 h (79–81%); vii, 80% AcOH, 100 °C, 1 h (51%); viii, $ClSO_2C_6H_4Me_3$, pyridine (60%)

† Optically pure material can be obtained by recrystallization.

carried through steps (v)–(vii) (NMR evidence). The pure lactone **15** was obtained by recrystallization (*vide supra*); alternatively, formation of the corresponding tosyl derivatives and chromatography yielded pure **16**.[16]

We believe that these studies have generated a simple method for the production of the (*R*)-sulfoxide **1** and have indicated how this sulfoxide can be converted into the lactone **15** in a straightforward manner, through a modification of the Heathcock [16] procedure.

Experimental

Chemicals for the medium were obtained from Oxoid Ltd. Methyl *p*-tolyl sulfide was obtained from Sigma Ltd. and AnalaR ethyl acetate from BDH. *Saccharomyces cerevisiae* NCYC 73 was obtained from The National Collection of Yeast Cultures, Norwich.

Cultivation of *Saccharomyces cerevisiae* NCYC 73

Saccharomyces cerevisiae NCYC 73 was grown on a medium composed of glucose (10 g), yeast extract (3 g), malt extract (3 g) and neutralised bacterial peptone (3g) per 1 dm^3 of distilled water adjusted to pH 6.2 with 2 mol dm^{-3} HCl. An inoculum of *Saccharomyces cerevisiae* NCYC 73 was grown in 25 cm^3 of medium for 24 h, transferred aseptically to 1 dm^3 for 24 h, and then grown in 10 dm^3 for 48 h at 25 °C without aeration. The thick white mat of yeast cells at the base of the vessel was harvested by centrifugation (5000 g for 30 min at 4 °C), washed once with 100 mmol dm^{-3} citrate/phosphate buffer pH 6.0, and finally resuspended in 1% glucose in this buffer at 12.5 times the concentration of the growing cells (0.125 g wet mass per cm^3 buffer).

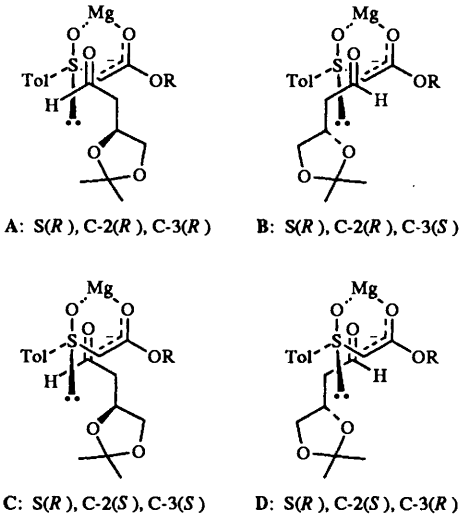


Fig. 1 Approach of the enolate to the aldehyde focussing on the interactions of the tolyl group and the lone-pair on the sulfur atom with the H-atom and methylene group attached to the carbonyl carbon atom

Synthesis of (*R*)-(+)-methyl *p*-tolyl sulfoxide by *Saccharomyces cerevisiae* NCYC 73

A solution of methyl *p*-tolyl sulfide in ethanol (200 mg cm^{-3}, 1.447 mol dm^{-3}) was prepared and added to the described culture of *Saccharomyces cerevisiae* NCYC 73 to a final concentration of 7.2 mmol dm^{-3}. The mixture was shaken at ambient temperature in an orbital shaker at 200 rpm. Synthesis of methyl *p*-tolyl sulfoxide was monitored by a BP1 non-polar GC column at 150 °C, and after 24–48 h the cells were removed by centrifugation. The supernatant solution was extracted with ethyl acetate (×2 volume) and the organic extract dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel with ethyl acetate as eluent. The solvent was evaporated under reduced pressure to yield the (*R*)-sulfoxide in 60% yield.

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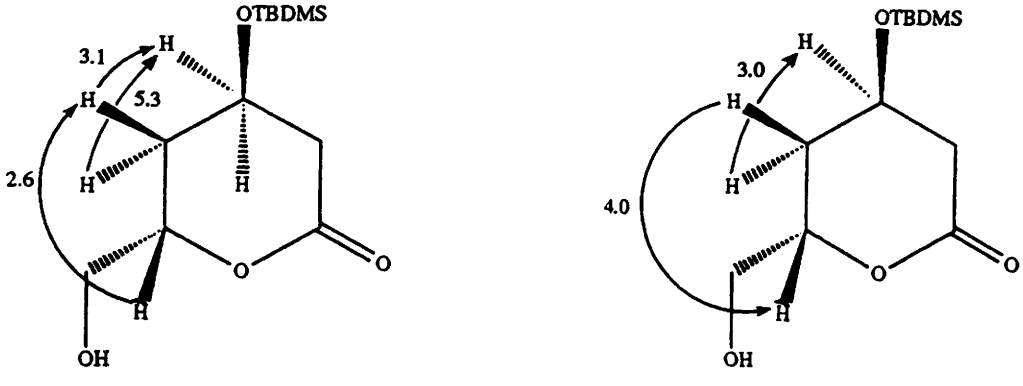

Fig. 2 Nuclear Overhauser enhancements for the lactone **15**. Values are quoted as percentage enhancements (Note there is no enhancement of the *trans* proton at C-4 to the C-3 proton on irradiation of C-3)

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