Article

Baker's Yeast Mediated Reduction of 2-Acetyl-3-methyl Sulfolane

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Abstract: The baker's yeast mediated reduction of 2-acetyl-3-methyl sulfolane **1** to provide the corresponding alcohol **2** is described. Excellent efficiency and enantioselectivity (>98% *ee*) has been achieved under these mild environmentally benign reaction conditions. In direct contrast, the chemical reduction of **1** proceeds with poor yield (≤25%) and diastereocontrol.

Keywords: baker's yeast (*Saccharomyces cerevisiae*); biocatalysis; asymmetric reduction; chiral alcohol; sulfolane

1. Introduction

One of the most widely studied and commercially significant whole cell systems employed in biocatalysis is baker's yeast (*Saccharomyces cerevisiae*), which has been extensively utilised in the asymmetric reduction of a wide variety of ketones. This is largely due to the ready availability, ease of experimental procedures and versatility of this microorganism [1–5]. Both the efficiency and stereoselectivity in baker's yeast mediated reduction of ketones is strongly influenced by both the presence and the position of sulfur substituents or indeed by the use of sulfur containing additives [6,7].

We have previously reported the successful optimisation of baker's yeast mediated reduction of 2-benzenesulfonyl substituted cyclopentanone and cyclohexanone derivatives to form the corresponding cycloalkanol in enantiopure form [8,9]. In addition, a viable route to the complementary enantiomeric series has been identified [10]. Base induced ring cleavage of the enantioenriched β-keto-sulfones has also been described to provide a synthetically viable route to enantioenriched novel carboxylic acids [10].

Leading on from the success of the enantioselective yeast reduction of cyclopentanones bearing α-benzenesulfonyl groups, we extended this study to include a five-membered cyclic sulfone (sulfolane) substituted at the 2- and 3-positon. The cyclic sulfone moiety is an important pharmacophore in medicinal chemistry. The ring structure has been explored as the key chiral subunit and scaffold for the construction of biologically active molecules for example protease and β-lactamase inhibitors [11–15].

The sulfolane structure is similar to that of the previously reported 2-benzenesulfonyl substituted cyclopentanone, except the sulfonyl moiety is incorporated within the ring structure with the ketone functionality external to the ring (Figure 1). In terms of relative positioning of the ketone and sulfonyl moieties it could not be anticipated if the sulfolane would fit into the active site of the reductase to facilitate hydride delivery to the carbonyl group. Herein, we report our studies, exploring the mild baker's yeast mediated reduction of 2-acetyl-3-methyl sulfolane **1**.

**Figure 1.** 2-Sulfonyl-3-methylcyclopentanone and 2-acetyl-3-methyl sulfolane **1**.

2. Results and Discussion

### 2.1. Preparation of trans-2-Acetyl-3-methyl Sulfolane *1*

The key to the synthesis of racemic *trans*-2-acetyl-3-methyl sulfolane **1**, the desired substrate for baker's yeast mediated reduction, was the initial preparation of sulfonylpropanone **5** which encompassed the basic acyclic system with both functional groups in the required position [16,17]. Highly regioselective carbenoid C–H insertion of α-diazocarbonyl compounds mediated by rhodium(II) was chosen as an excellent synthetic route for the subsequent ring closure to provide the tetrahydro-thiophene system (Scheme 1).

The intermolecular rhodium(II) catalysed C–H insertion reaction of α-diazo-β-keto sulfones has been widely developed by Monteiro [18] and this synthetic methodology has been extensively employed in our group in the preparation of the 3-susbtituted-2-benzenesulfonylcyclopentanones [8–10]. In this study $Rh_2(tfacam)_4$ gave excellent regioselectivity in the remote functionalisation of the unactivated C–H bond with one sulfolane diastereomer observed by ^{1}H NMR analysis. The relative stereochemistry of **1** was assigned as *trans* by NMR spectroscopy.

Scheme 1. Synthesis of *trans*-2-acetyl-3-methyl sulfolane **1**.
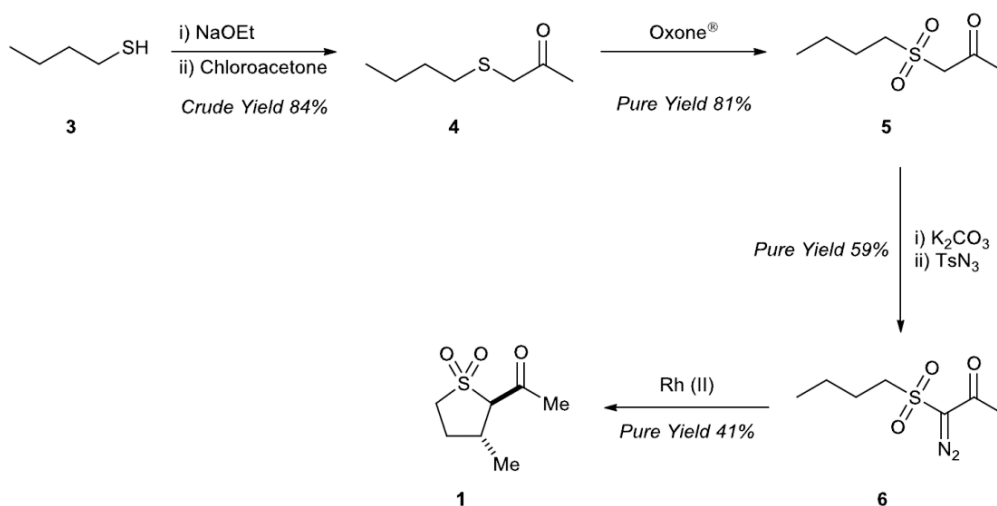
2.2. Sodium Borohydride Reduction of trans-2-Acetyl-3-methyl Sulfolane 1

Traditional sodium borohydride reduction of the diastereomerically pure *trans*-2-acetyl-3-methyl sulfolane **1** was remarkably inefficient. The recovered alcohol **2** was isolated in very low yield ((11%–25%), Table 1, entries 1–3). Significantly, when other reducing agents were investigated at various temperatures a similarly poor yield ((10%–15%), Table 1, entries 4–7) of alcohol **2** was recovered.

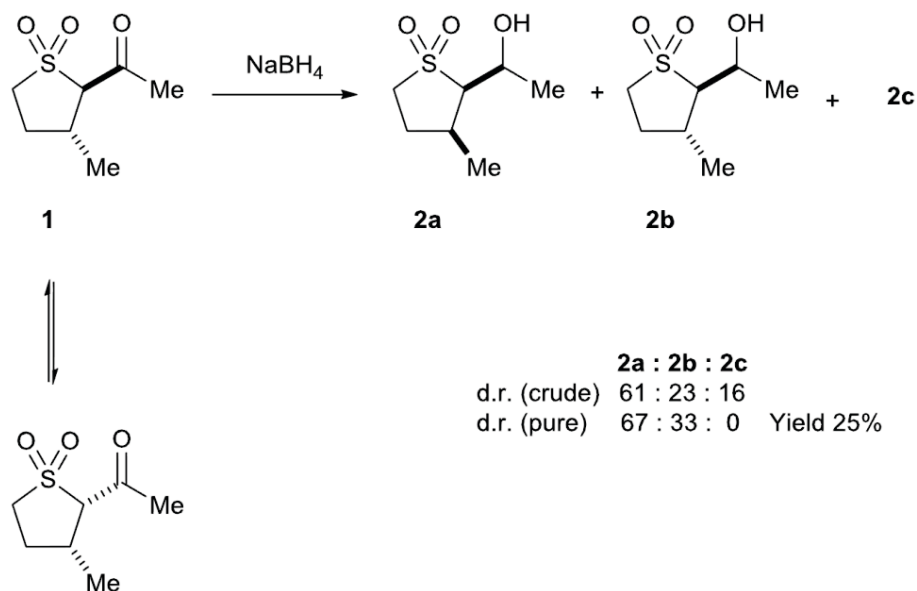**Table 1.** Chemical reduction of *trans*-2-acetyl-3-methyl sulfolane **1**.
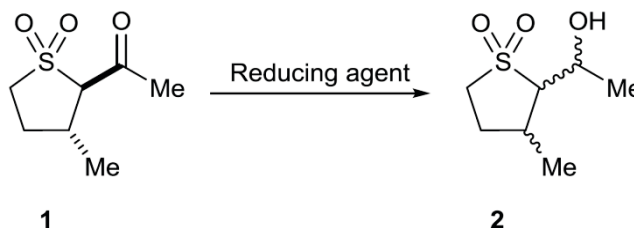
Entry [a]	Reducing Agent	Temperature	Yield 2 (%) [b]
1	NaBH$_4$/Ethanol	Room temperature	11
2	NaBH$_4$/Ethanol	0 °C	25
3	NaBH$_4$/Ethanol	−30 °C	20
4	NaBH$_3$CN/Methanol	Room temperature	10
5	LiAlH$_4$/Diethyl ether	0 °C	15
6	L-Selectride/THF	−78 °C	12
7	L-Selectride/THF	−78 °C to room temperature	12

[a] In all cases the starting material sulfolane **1** was added as a diastereomerically pure sample; [b] Yields quoted are following purification by column chromatography on silica gel.

Furthermore, the product **2** also displayed poor diastereocontrol. A mixture of three diastereomers in the ratio 61:23:16 (NaBH$_4$/Ethanol mediated reduction at 0 °C (Table 1, entry 2)) was evident in the ^{1}H NMR spectrum of the crude material. Following purification of this sample by column chromatography, only two of the isomers were detected **2a** and **2b**, and isolated as an inseparable mixture in the ratio 67:33 (Scheme 2). The poor efficiency and diastereoselectivity of the chemical mediated reduction was unprecedented as previously reported sodium borohydride reductions of the β-keto sulfones had

resulted in quantitative recovery of the required alcohols [8–10]. Relative stereochemistry on the sulfolane ring of the diastereomers **2a** and **2b**, was tentatively assigned by ^{1}H NMR spectral analysis however it was not possible to identify the relative stereochemistry at the hydroxyl centre. It is clear on the basis of the diastereomeric mixture recovered that partial epimerization of **1** to the corresponding *cis* isomer occurs in the reaction medium prior to reduction. As the β-keto sulfone is relatively acidic, interconversion of the *cis* and *trans* isomers is readily rationalized.

Scheme 2. Sodium borohydride reduction of *trans*-2-acetyl-3-methyl sulfolane **1**.


Clearly the conventional chemical route to the alcohol **2** is not synthetically practical; accordingly, the baker's yeast mediated reduction of *trans*-2-acetyl-3-methyl sulfolane **1** was next explored.

2.3. Baker's Yeast Reduction of trans-2-Acetyl-3-methyl Sulfolane 1

The baker's yeast mediated biocatalytic reduction of *trans*-2-acetyl-3-methyl sulfolane **1** was conducted employing a suspension of baker's yeast and sucrose in tap water at room temperature. The yeast reduction proceeded efficiently with two diastereomeric alcohols **2a** and **2b** (67% combined pure yield) and only a trace of starting material **1** (7% pure yield) isolated from the crude reaction mixture following purification by column chromatography (Scheme 3). This is in direct contrast to the chemical reduction of **1** which yielded a crude mixture of three diastereomers and a very poor recovery of the diastereomeric alcohols **2a** and **2b** following purification (25% combined pure yield).

The baker's yeast mediated reduction of *trans*-2-acetyl-3-methyl sulfolane **1** yielded two diastereomers **2a** and **2b**, isolated in the ratio 40:60. It is clear that in the yeast medium the *cis* and *trans* isomers of the sulfolane **1** interconvert via enolisation (Scheme 4). The yeast reductases selectively reduce these sulfolanes to form two diastereomeric alcohols, presumably reacting selectively with the ketone isomers bearing the same absolute stereochemistry at C-2. The yeast enzymes do not appear to distinguish the sterocentre at C-3. While the stereochemistry at C-2 and C-3 of the two diastereomers was not definitively confirmed in the study, based on Prelog's rule *S*-configuration at the newly generated stereogenic hydroxyl centre is envisaged in each case [19].

Scheme 3. Baker's yeast and NaBH₄ reduction of *trans*-2-acetyl-3-methyl sulfolane **1**.
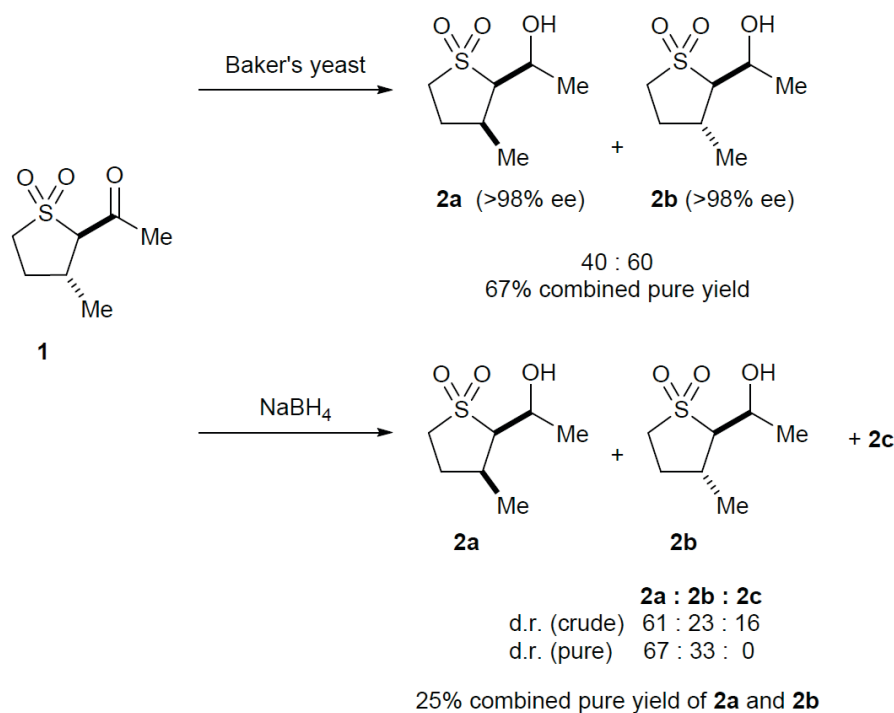
Scheme 4. Baker's yeast reduction of *trans*-2-acetyl-3-methyl sulfolane **1**.
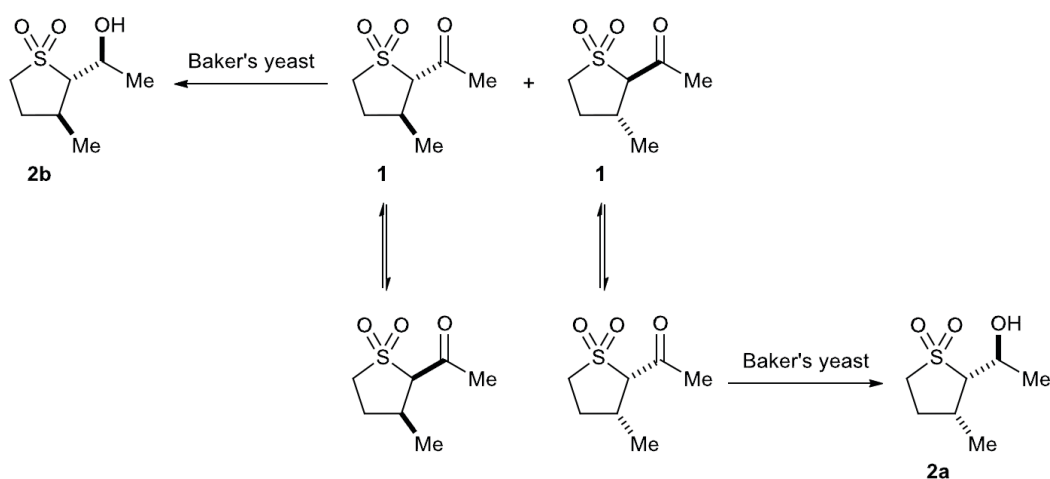
A number of strategies have been reported in the literature to improve the diastereoselectivity of baker's yeast, namely action of irreversible enzyme inhibitors [20–23], addition of organic solvents [24], cell immobilization [25–27], chemical modification of the substrate [28], pre-treatment of the cellular mass [29] and addition of sulfur compounds to the reaction mixture [30]. Interestingly, the diastereocontrol of the microbial reduction was opposite to the borohydride reduction, the principal isomer isolated being **2b** as opposed to **2a** in the chemical reduction.

Excellent enantiopurity of each of the generated alcohols **2a** and **2b** was attained (>98% *ee*). ¹H NMR spectroscopy in the presence of the chiral shift reagent Eu(hfc)₃, conducted on both racemic and enantiopure samples, determined that each of the products isolated **2a** and **2b** was enantiopure, demonstrating that baker's yeast was capable of effecting selective reduction. Thus, the sulfolane moiety can fit into the active site of the yeast reductase to facilitate hydride delivery to the carbonyl group.

3. Experimental Section

3.1. General

All solvents were dried and distilled prior to use. Organic phases were dried using anhydrous magnesium sulfate. 4-Toluenesulfonyl azide was prepared using extreme care from 4-toluenesulfonyl chloride and sodium azide in aqueous acetone [31]. In the baker's yeast reductions, the sucrose employed was obtained from Siúcra Irish Granulated Sugar (Dublin, Ireland); the antifoam solution employed was Antifoam 289 (pfs) (Gillingham, UK) mixed solution. Ordinary tap water was used as solvent and Sigma (Gillingham, UK) type II baker's yeast (BY; *Saccharomyces cerivisae*) was employed. All reactions were carried out under an inert atmosphere. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker (Billerica, MA, USA) Avance 300 NMR spectrometer. All spectra were recorded at room temperature (~20 °C) in deuterated chloroform (CDCl$_3$), using tetramethylsilane (TMS) as an internal standard. Enantiomeric purity was determined by ^{1}H MMR spectroscopy (300 MHz) in the presence of the chiral shift reagent *tris*[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] emporium(III) derivative [Eu(hfc)$_3$], added portionwise using ~8 mol%. Optical rotations were measured on a Perkin-Elmer (Waltham, MA, USA); 141 polarimeter at 589 nm in a 10 cm cell; concentrations (*c*) are expressed in g/100 mL. [α]$_D$ is the specific rotation of a compound and is expressed in units of 10^{-1} deg cm^2 g^{-1}. Elemental analysis was performed by the Microanalysis Laboratory, National University of Ireland, Cork, using Perkin-Elmer (Waltham, MA, USA); 240 elemental analyser. Melting points were carried out on a uni-melt Thomas Hoover Capillary (Philadelphia, PA, USA) melting point apparatus and are uncorrected. Infrared spectra were recorded as thin films on sodium chloride plates for oils or as potassium bromide (KBr) discs for solids on a Perkin Elmer (Dublin, Ireland); Paragon 1000 FT-IR spectrometer. 1-(Butanethio)propan-2-one **4** and 1-(butanesulfonyl)propan-2-one **5** have previously been reported in the literature [16,17].

3.2. 1-(Butanesulfonyl)-1-diazopropan-2-one 6

Potassium carbonate (1.52 g, 11.00 mmol) was added to a stirring solution of 1-(butanesulfonyl)propan-2-one **5** (1.78 g, 10.00 mmol) in acetonitrile (15 mL) at room temperature. The reaction mixture was stirred at room temperature for 10 min and then cooled to 0 °C by immersion of the reaction mixture into an ice-bath. A solution of 4-toluenesulfonyl azide (2.13 g, 10.80 mmol) in acetonitrile (15 mL) was added dropwise over 5 min. The reaction mixture was stirred for 2 h at 0 °C during which time the solution changed to orange in colour. Diethyl ether (20 mL) was then added to precipitate the insoluble salts. The orange suspension was filtered through a bed of Celite$^®$ (Sigma-Aldrich, Gillingham, UK) and washed with diethyl ether (10 mL). The filtrate was dried and concentrated at reduced pressure. A solution of hexane and diethyl ether (30 mL, 2:1) was added to the resulting residue and the mixture was stirred for 30 min. The resulting solution was filtered and the yellow filtrate was dried and concentrated at reduced pressure to give the crude diazo compound **6**. Purification of this crude product by column chromatography on silica gel using ethyl acetate-hexane (30:70) as eluent gave 1-(butanesulfonyl)-1-diazopropane-2-one **6** (1.20 g, 59%) as a yellow oil; v_{max}/cm^{-1} (film) 2117, 1667, 1332, 1139; δ$_H$ (CDCl$_3$, 300 MHz) 0.97 (3H, t, *J* = 7 Hz, C*H$_3$*-4'), 1.41–1.58 (2H, sym m, *J* = 7 Hz,

C*H*$_2$-3'), 1.77–1.90 (2H, m, C*H*$_2$-2') 2.39 (3H, s, COC*H*$_3$), 3.31–3.39 (2H, m, C*H*$_2$SO$_2$); δ$_C$ (CDCl$_3$, 75.5 MHz) 13.54 (CH$_3$, *C*H$_3$), 21.34 (CH$_2$, *C*H$_2$-3'), 24.70 (CH$_2$, *C*H$_2$-2'), 27.00 (CH$_3$, CO*C*H$_3$), 57.42 (CH$_2$, *C*H$_2$SO$_2$), 90.12 (C, *C*O).

3.3. trans-1-(3-Methyl-1,1-dioxo-tetrahydro-1λ^6-thiophen-2-yl)ethanone *1*

Rhodium(II) trifluoroacetamide (0.5 mg, 0.82 μmol, 0.05 mol%) was added to a refluxing solution of 1-(butanesulfonyl)-1-diazopropan-2-one **6** (300 mg, 1.47 mmol) in dichloroethane (10 mL). The progress of the reaction was monitored by IR spectroscopy, where reaction completion was indicated by the disappearance of the characteristic diazo peak at 2117 cm^{-1}, *ca*. 12 h. Upon reaction completion, the reaction mixture was cooled and evaporation of the reaction solvent at reduced pressure gave the crude product. Purification by column chromatography on silica gel using ethyl acetate-hexane (30:70) as eluent gave the pure sulfolane product **1** (106 mg, 41%) as a pale yellow solid, tentatively assigned as the *trans*-isomer (>98:2 d.r.); m.p. 53–55 °C; Found C, 47.83; H, 6.98; S, 18.01. C$_7$H$_{12}$SO$_3$ requires C, 47.71; H, 6.86; S, 18.20; ν$_{max}$/cm^{-1} (KBr) 2959, 1721, 1317, 1126; δ$_H$ (CDCl$_3$, 300 MHz) 1.15 (3H, d, *J* = 6.5 Hz, C*H*$_3$), 1.68–1.88 (1H, m, *H*$_A$ of C*H*$_2$-4), 2.25–2.37 (1H, m, *H*$_B$ of C*H*$_2$-4), 2.43 (3H, s, COC*H*$_3$), 2.76–2.82 (1H, sym m, *J* = 6 Hz, C*H*Me), 3.03–3.17 (1H, m, *H*$_A$ of C*H*$_2$-5), 3.28–3.37 (1H, m, *H*$_B$ of C*H*$_2$-5), 3.68 (1H, d, *J* = 10 Hz, SO$_2$C*H*CO); δ$_C$ (CDCl$_3$, 75.5 MHz) 19.12 (*C*H$_3$), 28.12, 31.59, 33.44 (*C*H$_2$-4, *C*HMe and CO*C*H$_3$), 53.39 (*C*H$_2$SO$_2$), 77.64 (SO$_2$*C*HCO), 197.24 (*C*O).

3.4. Reduction of *1* with Sodium Borohydride

1-(3-Methyl-1,1-dioxo-tetrahydro-1λ^6-thiophen-2-yl)ethanol **2**

The *trans*-2-acetyl-3-methyl sulfolane **1** (100 mg, 0.57 mmol) (>98:2 d.r.) in ethanol (10 mL) was added dropwise over 5 min to a suspension of sodium borohydride (39 mg, 1.02 mmol) in ethanol (10 mL) at 0 °C. The reaction mixture was stirred for 50 min at this temperature and then the ice bath was removed. Water was added (10 mL) to the reaction mixture and it was then concentrated at reduced pressure. The resulting residue was partitioned between diethyl ether (20 mL) and water (10 mL), the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (20 mL), dried and concentrated at reduced pressure to give the crude alcohol **2**. A ^{1}H NMR spectrum of the crude sample was recorded and showed the presence of a mixture of three isomers (61:23:16 d.r.), as determined by characteristic signals at δ$_H$ 3.91–4.07 (61%), δ$_H$ 4.17–4.26 (16%) and δ$_H$ 4.43–4.52 (23%). Purification of this crude product by chromatography on silica gel using ethyl acetate-hexane (50:50) as eluent gave **2** (26 mg, 25%) as a colourless oil and as an inseparable mixture of two diastereomers, *cis*-2-ethanol-3-methyl sulfolane **2a** and *trans*-2-ethanol-3-methyl sulfolane **2b**, (67:33 d.r.) which was contaminated with a trace amount (~8%) of an unidentified impurity; ν$_{max}$/cm^{-1} (KBr) 3500, 1312, 1125; δ$_H$ (CDCl$_3$, 300 MHz) 1.22 (2.01H, d, *J* = 6, C*H*$_3$-3 of **2a**), 1.28 (0.99H, d, *J* = 7, one of C*H*$_3$ of **2b**), 1.32 (0.99H, d, *J* = 7 Hz, one of C*H*$_3$ of **2b**), 1.51 (2.01H, d, *J* = 7 Hz, CH(OH)C*H*$_3$ of **2a**), 1.68–1.82 (1H, one of C*H*$_2$-4), 2.20–2.32 (1H, m, one of C*H*$_2$-4), 2.33–2.47 (0.67H, sym m, *J* = 6 Hz, C*H*Me of **2a**), 2.51–2.73 (1.33H, m, one of C*H*$_2$-5 and C*H*Me of **2b**), 2.82–3.07 (1H, m, SO$_2$C*H*), 3.07–3.25 (1H, m, one of C*H*$_2$-5), 3.96–4.08 (0.67H, m, C*H*OH of **2a**), 4.47 (0.33H, dq, *J* = 7 Hz, <1, C*H*OH of **2b**);

Major diastereomer, **1**; δ_C (CDCl$_3$, 75.5 MHz) 19.6 (CH$_3$, *C*H$_3$), 21.60 (CH$_3$, CH(OH)*C*H$_3$), 29.05 (CH$_2$, *C*H$_2$-4), 34.57 (CH, *C*HMe), 52.97 (CH$_2$, *C*H$_2$-5), 66.22, 73.39 (*C*H, *C*HOH and SO$_2$*C*H). Minor diastereomer, **2b**; δ_C (CDCl$_3$, 75.5 MHz) 20.89 (CH$_3$, *C*H$_3$), 22.17 (CH$_3$, CH(OH)*C*H$_3$), 29.05 (CH$_2$, *C*H$_2$-4), 31.04 (CH, *C*HMe), 51.93 (CH$_2$, *C*H$_2$-5), 64.35, 72.11 (*C*H, *C*HOH and SO$_2$*C*H).

*3.5. Reduction of **1** with Baker's Yeast*

1-(3-Methyl-1,1-dioxo-tetrahydro-1λ^6-thiophen-2-yl)ethanol **2**

A suspension of baker's yeast (Sigma, Type II, 10 g), sucrose (10 g) and antifoam (2 drops) in tap water (60 mL) was shaken gently at 28 °C for 30 min. *trans*-2-Acetyl-3-methyl sulfolane **1** (100 mg, 0.57 mmol) (>98:2 d.r.) in DMSO (1.5 mL) was added slowly over 1 minute and the mixture was shaken gently at 28 °C for 48 h. Celite® (5 g) (Sigma-Aldrich, Gillingham, UK) was then added and the mixture was stirred at room temperature for 30 min. The yeast mixture was filtered through a pad of Celite® and washed with water (50 mL) and ethyl acetate (50 mL). The filtrate was separated and the aqueous layer was saturated with sodium chloride and extracted with ethyl acetate (3 × 100 mL). The organic layers were combined and washed with brine (75 mL), dried and concentrated at reduced pressure to give the crude alcohol **2** as a yellow oil. Purification by column chromatography on silica gel using ethyl acetate-hexane (35:75) as eluent gave the unreacted *trans*-2-acetyl-3-methyl sulfolane **1** (7 mg, 7%) and an inseparable mixture of *cis*-2-ethanol-3-methyl sulfolane **2a** and *trans*-2-ethanol-3-methyl sulfolane **2b** (62 mg, 61%) as a colourless oil, 40:60 d.r.: [α]$_D$ +19° (c 1, CHCl$_3$); >98% *ee*. for each diastereomer (as determined by ^{1}H NMR in the presence of Eu(hfc)$_3$). Spectral characteristics of the ethanone **1** and ethanol products **2a** and **2b** were in agreement with those of the racemic compounds.

4. Conclusions

In summary, the chemical reduction of 2-acetyl-3-methyl sulfolane **1** was not synthetically practical as the reduction proceeded with poor efficiency and diastereoselectivity. Significantly, efficient reduction of **1** was achieved utilising mild baker's yeast mediated reaction conditions providing the corresponding diastereomeric alcohols **2a** and **2b** in excellent enantiopurity (>98% *ee*) and good yield (67%). Thus, in this instance biocatalysis offers a higher degree of selectivity and efficiency relative to its conventional chemical counterpart. The enantiomerically pure alcohols **2a** and **2b** are valuable chiral synthons in synthesis, as both the hydroxyl and sulfonyl moieties are synthetically versatile.

Author Contributions

Conflicts of Interest

The authors declare no conflict of interest.

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