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Baker's yeast mediated biohydrogenation of sulphur-functionalised methacrolein derivatives. Stereochemical aspects of the reaction and preparation of the two enantiomers of useful C_4 bifunctional chiral synthons

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Abstract—The baker's yeast mediated reduction of sulphur-functionalised methacroleins **11**, **15** and **18** leads to the preparation of the bifunctional methyl branched C_4 chiral synthons **6** and **7**. The stereochemical aspects of the biohydrogenation have been investigated. Both the oxidation state of sulphur and the isomeric position of the double bond affected the enantioselectivity of the reduction strongly, thus, offering access to the two enantiomeric forms of **6** and **7**.

1. Introduction

The use of small (C_3, C_4, C_5) and readily available chiral building blocks in the preparation of complex enantiomerically pure compounds is one of the most employed synthetic strategies. In this context, 2-methyl branched chiral C_4 compounds of the type **1** are particularly suited for the synthesis of many biologically active substances possessing at least one tertiary carbon centre, typical of terpenoids and natural products of propionate biosynthetic derivation.

Several enantioselective syntheses of the above mentioned synthon have been developed with the use of biocatalysts. The asymmetrised 2-methyl-1,3-propanediols **2** are the most used compounds[1] of this class since they are efficiently prepared either from the commercially available (*S*) and (*R*)-3-hydroxy-2-methylpropanoic acid **3** and through different biocatalytic approaches.[1,2] Due to this fact, the activated forms of synthon **1** in which X or Y are functional groups able to give chain elongation, are prepared mainly from **2** and **3** by means of functional group manipulation (Fig. 1).

Herein, we wish to report the enantioselective preparation of useful bifunctional C_4 building block of type **1** by baker's yeast-mediated reduction of substituted methacrolein of type **4** and **5**. We selected the phenylthio and the phenylsulfonyl groups as β-substituents of these aldehydes (RX = PhS or $PhSO_2$) since compounds of the type **6** and **7** have been already

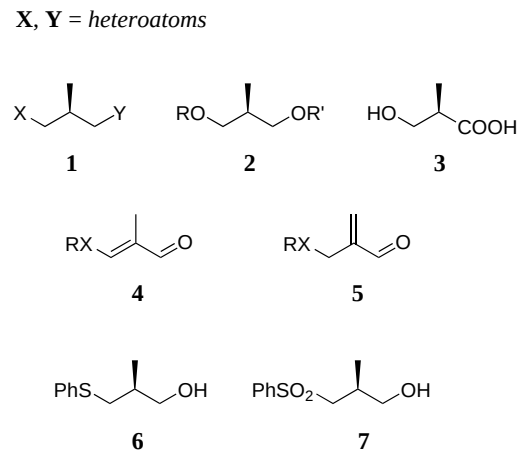

Figure 1.

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employed in several synthetic applications[3–5] and are well suited to chain elongation reactions, for instance by the Julia olefination protocol[4] or alkylation–desulphurisation sequences.[5] Until recently, these compounds were prepared from synthons of the type **2**[1,2a] and **3**,[3a,b,d,4,5] using enzyme-catalysed kinetic resolution[2a] or by auxiliary-based diastereoselective alkylation of chiral amide enolates.[3c] The enantioselective synthesis of **6** and **7** from sulphur-functionalized prochiral methacroleins compares favourably with these known methods since the aldehydes **4** and **5** are inexpensive and the problems related to functional group interconversion are overcome.

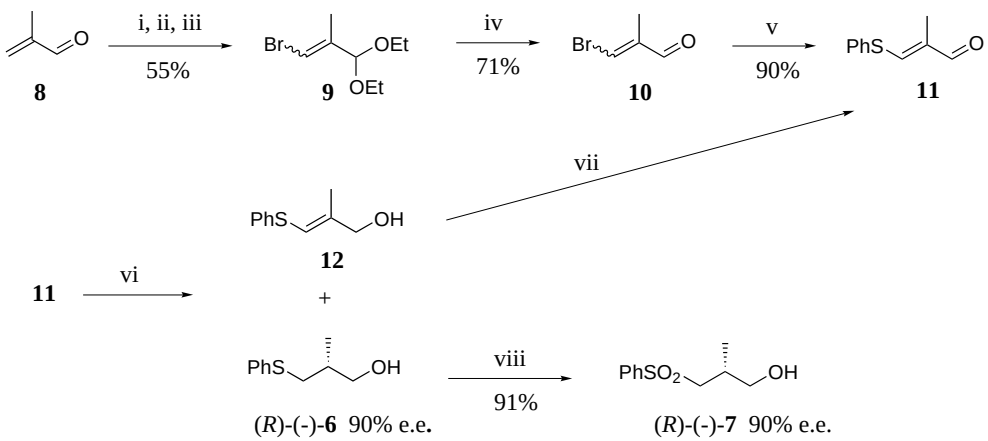
2. Results and discussion

The baker's yeast-mediated asymmetric reduction of a variety of sulphur funtionalised α,β-unsaturated aldehydes and ketones has been widely studied in the past.[6] Moreover, in order to obtain a C_5 chiral building block for the synthesis of isoprenoids, many α,β-unsaturated aldehydes or alcohols substituted with phenylsulfonyl, dithianyl or phenylthio groups were reduced[7] using yeast. In spite of this, to our knowledge, the microbial reduction of sulphur substituted methacroleins of the type **4** and **5** were not investigated previously.

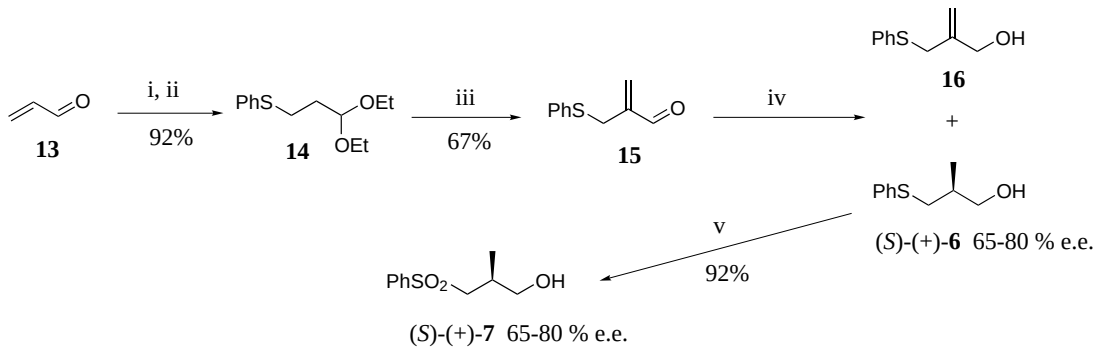
With the aim of preparing the C_4 chiral building block **6** on a multigram scale, we envisaged that phenylthio substituted methacroleins could be easily prepared from inexpensive and commercially available compounds. Accordingly, aldehyde **11** was prepared as depicted in Scheme 1. Methacrolein **8** was converted stepwise to the 3-bromoacrolein diethylacetal **9** by a known method.[8] Addition of bromine to **8**, protection of the carbonyl group and basic elimination of hydrogen bromide afforded **9** as a mixture of regioisomers. Subsequent hydrolysis of the acetal functionality gave the 3-bromo-acrolein **10** which was converted without isolation into aldehyde **11** by treatment with sodium thiophenate in THF solution.[9] Interestingly enough, **11** was obtained as a single (*E*) isomer.

In order to devise a large scale method for the preparation of homochiral **6** we performed the baker's yeast incubation of the above mentioned aldehyde supported on a non-polar resin.[10] This method shows several advantages since it allowed us to conduct the reduction on a hundred grams scale with a concentration of 10–15 g/L with a simple work-up procedure (see Section 4). We found that after 4 days of fermentation, **11** was reduced to a mixture of allylic alcohol **12** (64%), saturated alcohol **6** (25%) and starting aldehyde **11** (6%). Prolonging the incubation time, a slow (about 3% for each day) saturation of alcohol **12** increased the ratio of **6**. In order to obtain pure saturated alcohol we converted selectively the allylic alcohol to the starting aldehyde by MnO_2 oxidation of the crude mixture. The aldehyde **11** was recovered in 69% yield and can be recycled whilst alcohol **6** was separated in 22% of yield and was converted into synthon **7** by oxidation with MCPBA. The obtained **6** showed negative sign of optical rotation ($[\alpha]_D^{20} = -18.5$ (*c* 1, CH_2Cl_2), Ref. 3c $[\alpha]_D^{20} = -18.9$ (*c* 3.5, CH_2Cl_2)) and thus was assigned (*R*)-configuration in accord with the general trend of reduction of prochiral double bonds.[6a] The enantiomeric excess of (*R*)-(−)-**6** was evaluated as 90% by NMR analysis of its (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester).[11]

The study on the mode of yeast reduction of these sulphur-functionalised methacroleins was subsequently extended to aldehydes of the type **5**. Accordingly, we synthesised aldehyde **15** from acrolein **13** (Scheme 2) through known procedures which involved base-catalysed 1,4-addition[12a] of thiophenol to **13**, protection of the obtained aldehyde as its diethylacetal **14** and methylenation of the latter by Mannich type reaction.[12b] Thus, **15** was incubated with baker's yeast under the same experimental conditions described above for **11**. We observed completely different behaviour both in terms of yield and enantioselectivity. The double bond of the methacrolein **15** was saturated readily and after four days of fermentation the expected (*S*)-(+)-**6** (40%) was the main product together with allylic alcohol **16** (35%) and a small amount of residual



Scheme 1. (i) Br_2, CH_2Cl_2; (ii) $CH(OEt)_3$, EtOH, PTSA cat.; (iii) KOH, EtOH; (iv) H_2O, PTSA cat.; (v) PhSNa, THF; (vi) baker's yeast, 4 days; (vii) MnO_2, $CHCl_3$, reflux; (viii) MCPBA, CH_2Cl_2.



Scheme 2. (i) PhSH, Et_3N cat.; (ii) $CH(OEt)_3$, PTSA cat.; (iii) $Et_2NH.HCl$, CH_2O aq. reflux; (iv) baker's yeast, 4 days; (v) MCPBA, $CHCl_3$.

unsaturated aldehyde **15** (10%). Thus, the alcohol (*S*)-(+)-**6** and the related sulfone (*S*)-(+)-**7** were prepared from **15** in 36 and 33% overall yield, respectively. In spite of this efficiency of the reduction step, the enantiomeric purity of the above (*S*)-(+)-**6** (also measured by NMR analysis of its MTPA ester) was only 65% e.e., whereas when fermentation was interrupted after only 48 h the isolated **6** had greater e.e. of 80%.

These ambiguous results can be explained by considering that the heteroatom may assist the double bond isomerisation by conjugation. The following reduction of isomerised aldehyde affords the opposite enantiomer (*R*)-(−)-**6** lowering the enantiomeric purity of the product. In order to demonstrate our explanation and also in the aim of preparing (*S*)-(+)-**7** in good enantiomeric purity, we decided to study the reduction of aldehyde **18** (Scheme 3) in which double bond isomerisation is disfavoured by the presence of the phenylsulfonyl group. The latter compound was prepared from aldehyde **15** by conversion into ketal **17**, oxidation of the thiophenyl group to phenylsulfonyl and deprotection of the acetal functionality.

The yeast reduction of methacrolein **18** provided the allylic alcohol **19** (40%), (*S*)-(+)-**7** (40%), and unreacted **18** (15%). The obtained (*S*)-(+)-**7** was isolated in 20% overall yield and showed very high enantiomeric excess since, in NMR analysis of its MTPA ester, only the (*S*) isomer was detected (1% sensitivity so e.e. >98%).

3. Conclusions

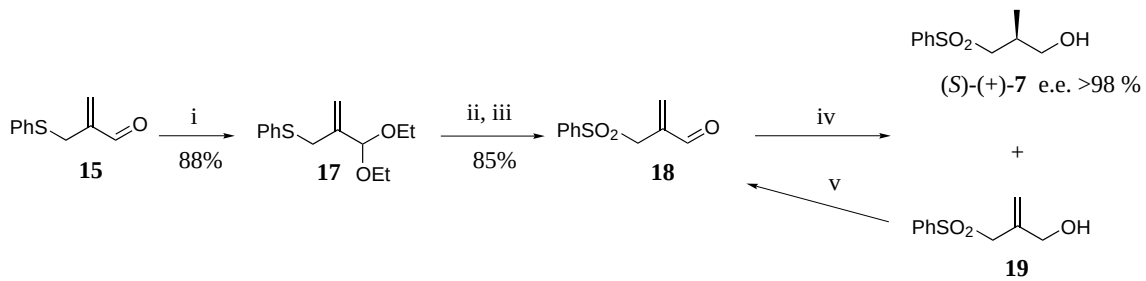
A study on the baker's yeast-mediated reduction of sulphur-functionalised methacroleins is reported. We found that the stereochemical behaviour of the double bond biohydrogenation depends on the position of the double bond and also on the oxidation state of sulphur. Taking advantage of this versatility we selected the aldehydes **11**, **15** and **18** as suitable precursors for the preparation of the bifunctional methyl branched C_4 chiral synthons **6** and **7**. Using our synthetic pathway and combining enzymatic manipulations with chemical ones, both enantiomeric forms of **6** and **7** were prepared in good yields.

Seen together, these results show that the use of baker's yeast in organic synthesis, although widely applied, still affords some new applications providing that the relevant synthetic targets are investigated.

4. Experimental

4.1. General methods

^1H NMR spectra were recorded in $CDCl_3$ solution at room temperature unless otherwise stated, on a Bruker AC-250 spectrometer (250 MHz ^1H). The chemical-shift scale is based on internal tetramethylsilane. IR spectra were recorded on a Perkin–Elmer 2000 FTIR spectrometer. Mass spectra were measured on a Finnigan-MAT TSQ 70 spectrometer. Melting points were



Scheme 3. (i) $CH(OEt)_3$, PTSA cat.; (ii) MCPBA, $CHCl_3$; (iii) H_2O/THF, PTSA cat.; (iv) baker's yeast, 4 days; (v) MnO_2, $CHCl_3$, reflux.

measured on a Reichert melting-point apparatus, equipped with a Reichert microscope, and are uncorrected. Optical rotations were determined on a Propol automatic digital polarimeter. Microanalyses were determined on an Analyser 1106 Carlo Erba. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. All chromatographic separations were carried out on silica gel columns. All baker's yeast biotransformations were performed using fresh baker's yeast (Marca Distillerie Italiane) commercially available from LIEVITALIA S.p.a.

4.2. Synthesis of the substrates

4.2.1. (*E*)-3-Thiophenyl-2-methylpropen-1-al 11[13]. Bromine (91 mL, 1.77 mol) was added dropwise to a stirred solution of methacrolein **8** (145 mL, 1.76 mol) in CH_2Cl_2 (250 mL) maintaining the temperature below 10°C by external cooling (ice bath). The resulting mixture was diluted with ethanol (100 mL), was treated with PTSA (1 g, 5 mmol). Triethyl orthoformate (320 mL, 1.92 mol) was then added in a few portions. The cooling bath was then removed and the reaction mixture was stirred at room temperature overnight. The resulting solution was washed with saturated $NaHCO_3$ (100 mL) and concentrated under reduced pressure. The obtained oil was dissolved in ethanol (300 mL) and treated with ethanolic KOH (110 g, 1.96 mol KOH in 250 mL) under reflux for 3 h. After cooling, the reaction was quenched with ice and extracted with diethyl ether (3×200 mL). The combined organic phases were concentrated in vacuo and the residue was distilled to give **9**[8] (216 g, 969 mmol, 55%) as an *E*/*Z* mixture (3:1 by GC analysis). Water (400 mL) and PTSA (1 g, 5 mmol) were added to **9** and the resulting heterogeneous mixture was heated at 80°C stirring for 20 min. The reaction was then cooled and extracted with diethyl ether (2×200 mL). The organic phase was washed with brine and concentrated under reduced pressure. The obtained crude **10**[8] (3:1 *E*/*Z* mixture, 102 g, 685 mmol, 71%), was added to a stirred suspension of sodium thiophenate (0.7 mol), prepared from thiophenol (77.2 g, 0.7 mol) and NaH (28.1 g of a 60% suspension in oil, 702 mmol), in dry THF. The mixture was stirred for 2 h at room temperature and then poured in ice and extracted with diethyl ether (2×200 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by distillation to give pure (98% GC) **11**[13] as a colourless oil (110 g, 618 mmol, 90%): bp 116°C (0.2 mmHg); ^{1}H NMR (δ ppm): 9.31 (1H, s, C*H*O), 7.54–7.35 (6H, m, Ar*H*+C*H*=C), 1.87 (3H, d, J=0.8 Hz, *Me*C); m/z (EI): 179 (M^++1, 10), 178 (M^+, 75), 177 (M^+–1, 31), 149 (5), 134 (12), 115 (9), 110 (100), 100 (10), 77 (9); FT-IR (film) 1667, 1582, 1482, 1441, 1327, 1177, 1019, 817, 744 cm^{-1}. Anal. calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65. Found: C, 67.45; H, 5.65%.

4.2.2. 3-(Phenylthio)-2-methylenepropan-1-al 15[12b]. Thiophenol (121 g, 1.1 mol) was added dropwise to a CH_2Cl_2 (350 mL) solution of acrolein **13** (80 mL, 1.2 mol) and triethylamine (1 mL, 7 mmol) stirring at 0°C for 1 h. In order to remove the amine, the obtained mixture was concentrated under reduced pressure and dissolved again in CH_2Cl_2 (200 mL). The solution was treated with PTSA (1 g, 5 mmol) and triethyl orthoformate (200 mL, 1.2 mol) at room temperature for 4 h. The reaction was then diluted with further CH_2Cl_2 (300 mL), quenched with saturated $NaHCO_3$ (100 mL) and washed with brine. The organic phase was separated, was dried (Na_2SO_4) and was concentrated in vacuo. Distillation of the residue gave pure (98% GC) 3-(thiophenyl)propionaldehyde diethyl acetal **14**[12a] as a colourless oil (243 g, 1.01 mol, 92%): bp 145°C (0.4 mmHg); ^{1}H NMR (δ ppm): 7.38–7.11 (5H, m, Ar*H*), 4.63 (1H, t, J=5.6 Hz, C*H*(OEt)$_2$), 3.72–3.57 (2H, m, OC*H*$_2$CH$_3$), 3.55–3.40 (2H, m, OC*H*$_2$CH$_3$), 2.98 (2H, t, J=7.4 Hz, PhSC*H*$_2$CH$_2$), 2.00–1.89 (2H, m, PhSCH$_2$C*H*$_2$), 1.20 (6H, t, J=6.9 Hz, OCH$_2$C*H*$_3$); m/z (EI): 240 (M^+, 34), 194 (M^+–EtOH, 29), 149 (23), 137 (9), 123 (100), 110 (32), 103 (52), 85 (77), 75 (39), 57 (35); FT-IR (film) 2976, 1585, 1482, 1439, 1373, 1127, 1063, 739, 691 cm^{-1}. Anal. calcd for $C_{13}H_{20}O_2S$: C, 64.96; H, 8.39. Found: C, 64.90; H, 8.40%.

The acetal **14** was combined with 36% aq. formalin (170 g, 2.04 mol), $Et_2NH{\cdot}HCl$ (224 g, 2.04 mol), hydroquinone (1 g, 9 mmol) and was stirred at 100°C for 3 h. The reaction mixture was poured into ice water followed by extraction with diethyl ether (3×200 mL). The organic layer was washed with saturated $NaHCO_3$ solution (2×100 mL), was dried (Na_2SO_4) and was concentrated in vacuo. The residue was purified by distillation to give pure (96% GC) aldehyde **15**[12b] (121 g, 0.68 mol, 67%) as a colourless oil: bp 115°C (0.6 mmHg); ^{1}H NMR (δ ppm): 9.56 (1H, s, C*H*O), 7.34–7.14 (5H, m, Ar*H*), 6.27 (1H, t, J=1.1 Hz, C=C*H*H), 6.04 (1H, s, C=CH*H*), 3.71 (2H, d, J=1.1 Hz, PhSC*H*$_2$C); m/z (EI): 179 (M^++1, 10), 178 (M^+, 84), 177 (M^+–1, 14), 160 (8), 145 (12), 134 (9), 116 (19), 110 (57), 91 (5), 84 (6), 77 (13), 68 (100); FT-IR (film) 1684, 1583, 1481, 1439, 1320, 955, 741, 692 cm^{-1}. Anal. calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65. Found: C, 67.30; H, 5.67%.

4.2.3. 3-(Phenylsulfonyl)-2-methylenepropan-1-al 18[14a]. The aldehyde **15** (63 g, 354 mmol) was dissolved in triethyl orthoformate (200 mL, 1.2 mol) and the solution treated with PTSA (1 g, 5 mmol) and hydroquinone (0.5 g, 4.5 mmol) stirring at 50°C for 3 days. After this time the mixture was concentrated under reduced pressure, the residue was diluted with diethyl ether (400 mL) and washed with a solution of saturated $NaHCO_3$ (100 mL). The organic phase was concentrated in vacuo and the residue was purified by chromathography eluting with hexane–ethyl acetate (95:5) to give pure (97% GC) 3-(thiophenyl)-2-methylene-propionaldehyde diethyl acetal **17**[14b] as a colourless oil (79 g, 313 mmol, 88%): ^{1}H NMR (400 MHz, δ ppm: 7.36–7.30 (2H, m, Ar*H*), 7.28–7.22 (2H, m, Ar*H*), 7.18–7.12 (1H, m, Ar*H*), 5.30 (1H, s), 5.21 (1H, s), 4.96 (1H, s), 3.66–3.57 (2H, m, OC*H*$_2$CH$_3$), 3.64 (2H, s, PhSC*H*$_2$C), 3.52–3.43 (2H, m, OC*H*$_2$CH$_3$), 1.22 (6H, t, J=7 Hz, OCH$_2$C*H*$_3$); m/z (EI): 252 (M^+, 21), 207 (16), 173 (32), 161 (100), 149 (23), 142 (73), 114 (70), 86 (36), 69 (46); FT-IR (film) 2976, 1584, 1482, 1439, 1115, 1062, 923, 739, 691 cm^{-1}. Anal. calcd for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99. Found: C, 66.70; H, 8.02%.

The acetal **17** was dissolved in CH_2Cl_2 (200 mL) cooled at −78°C and treated under stirring with a solution of MCPBA (160 g of a 70% commercial reagent, 649 mmol) in CH_2Cl_2 (250 mL) over 1 h. The reaction mixture was allowed to warm to room temperature and was stirred for further 2 h. The MCBA was eliminated by filtration and the solution was washed in turn with saturated $NaHCO_3$ solution (2×100 mL), and 5% aq. Na_2SO_3 (100 mL). The organic layer was concentrated under reduced pressure and the residue was dissolved in a THF/water (5:1) mixture (200 mL). The obtained solution was treated with PTSA (1 g, 5 mmol) stirring at rt for 2 h. After this time the reaction was quenched by addition of water and extraction with ethyl acetate (3×150 mL). The organic phase was washed with brine, was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography eluting with hexane–ethyl acetate (9:1→7:3) to give pure (99% GC) **18**[14a] as colourless crystals (56 g, 267 mmol, 85%): mp 69°C (hexane/ethyl acetate); ^{1}H NMR (δ ppm): 9.36 (1H, s, C*H*O), 7.89–7.81 (2H, m, Ar*H*), 7.70–7.61 (1H, m, Ar*H*), 7.59–7.50 (2H, m, Ar*H*), 6.76 (1H, s, C=C*H*H), 6.41 (1H, s, C=C*H*H), 4.11 (2H, s, SO_2CH_2C); *m*/*z* (EI): 210 (M^+, 1), 192 (3), 175 (2), 163 (2), 141 (51), 125 (28), 115 (5), 77 (100), 69 (30), 51 (23); FT-IR (nujol) 1682, 1332, 1305, 1250, 1168, 1134, 1086, 979, 903, 856, 801, 761, 713, 690 cm^{-1}. Anal. calcd for $C_{10}H_{10}O_3S$: C, 57.13; H, 4.79. Found: C, 57.10; H, 4.80%.

4.3. Baker's yeast (BY) biotransformations

4.3.1. General procedure. *Representative example on 100 g scale performed for the reduction of **11**:* A 10 litre open cylindrical glass vessel equipped with a mechanical stirrer was charged with tap water (6 L) and glucose (350 g). Fresh BY (1 Kg) was added in small pieces to the stirred mixture and fermentation allowed to proceed for 1 h. The aldehyde **11** (100 g, 562 mmol), adsorbed on XAD 1180 resin (400 g), was added in one portion. The mixture was vigorously stirred for 4 days at room temperature. During this time additional BY (250 g) and glucose (100 g) were added 24 and 48 h after fermentation started. The resin was separated by filtration on a sintered glass funnel (porosity 0, >160 μm) and the water phase extracted again with further resin (100 g). The combined resin crops were extracted with ethyl acetate (5×200 mL) and the acetate solution was washed with brine. The dried organic phase (Na_2SO_4) was concentrated under reduced pressure to give an oil. This latter was composed of saturated alcohol (25%) together with unreacted aldehyde (6%) and the related unsaturated allylic alcohol **12** (64%), also produced by microbiological reduction. In order to obtain pure saturated alcohol we converted selectively the allylic alcohol into the starting aldehyde by MnO_2 oxidation. The crude mixture was dissolved in $CHCl_3$ and treated with MnO_2 (200 g) stirring under reflux until no more allylic alcohol was detected by GC analysis (12 h). The residue obtained upon filtration and evaporation of the $CHCl_3$ phase was purified by column chromatography using hexane–ethyl acetate (95:5→8:2) as eluent to give recovery aldehyde **11** (69 g after distillation, 388 mmol, 69%) and alcohol **6** (22.4 g after distillation, 123 mmol, 22%)

4.3.2. (*R*)-(−)-2-Methyl-3-(phenylthio)propan-1-ol 6[2a,b,3,a,c] **by BY reduction of 11**. Obtained as described above as a colorless oil (99% GC): bp 118–120°C/0.2 mmHg; $[\alpha]_D^{20}=-18.5$ (*c* 1, CH_2Cl_2); e.e. = 90%; Ref. 2a $[\alpha]_D^{25}=-19.9$ (*c* 1.4, CH_2Cl_2); Ref. 2b $[\alpha]_D^{20}=-13.8$ (*c* 3, CH_2Cl_2); Ref. 3c $[\alpha]_D^{20}=-18.9$ *c* 3.5, CH_2Cl_2); ^{1}H NMR (δ ppm): 7.38–7.22 (4H, m, Ar*H*), 7.20–7.12 (1H, m, Ar*H*), 3.66–3.53 (2H, m, CHC*H*$_2$OH), 3.06 (1H, dd, *J* = 12.9, 6.9 Hz, SC*H*HCH), 2.82 (1H, dd, *J* = 12.9, 6.9 Hz, SCH*H*CH), 2.04–1.84 (1H, m, CH_3CH), 1.83 (1H, s, O*H*), 1.04 (3H, d, *J* = 6.8 Hz, C*H*$_3$CH); *m*/*z* (EI): 183 (M^++1, 8), 182 (M^+, 68), 164 (1), 149 (4), 123 (38), 110 (100), 91 (5), 84 (3), 77 (8), 72 (9), 65 (9), 57 (10); FT-IR (film) 3355, 1584, 1481, 1438, 1026, 738, 691 cm^{-1}. Anal. calcd for $C_{10}H_{14}OS$: C, 65.89; H, 7.74. Found: C, 65.96; H, 7.75%.

4.3.3. (*S*)-(+)-2-Methyl-3-(phenylthio)propan-1-ol 6[4b] **by BY reduction of 15**. The BY reduction of **15** (50 g, 280 mmol) afforded a mixture of alcohol **6** (40%), alcohol **16** (35%) starting aldehyde **15** (10%), and isomerised alcohol **12** (4%). MnO_2 oxidation, purification by chromatography and distillation gave pure (98% GC) (*S*)-(+)-**6** (18.2 g, 100 mmol, 36%) as a colourless oil: $[\alpha]_D^{20}=+13.3$ (*c* 1.2, CH_2Cl_2); e.e. = 65%; a similar reduction (30 g, 168 mmol) performed with an incubation of 48 h afforded (*S*)-(+)-**6** (6.2 g, 34 mmol, 20%); $[\alpha]_D^{20}=+15.9$ (*c* 1.2, CH_2Cl_2); e.e. = 80% (the optical rotation value for (*S*)-(+)-**6** has not been previous reported); both sample of (*S*)-(+)-**6** show analytical data identical to those above reported for (*R*)-(−)-**6**.

4.3.4. (*S*)-(+)-2-Methyl-3-phenylsulfonylpropan-1-ol 7 by BY reduction of 18. The BY reduction of **18** (40 g, 190 mmol) afforded a mixture of alcohol **19** (40%), alcohol **7** (40%) and starting aldehyde **18** (15%). MnO_2 oxidation and purification by chromatography gave aldehyde **18** (11.1 g, 53 mmol, 28%) and pure (98% GC) (*S*)-(+)-**7** (8.15 g, 38 mmol, 20%) as a pale yellow oil: $[\alpha]_D^{20}=+9.3$ (*c* 1.1, $CHCl_3$); e.e. >98% (the optical rotation value for (*S*)-(+)-**7** has not been previously reported); ^{1}H NMR (δ ppm): 7.96–7.88 (2H, m, Ar*H*), 7.71–7.52 (3H, m, Ar*H*), 3.69 (1H, dd, *J* = 10.9, 4.9 Hz, SO_2CH*H*CH), 3.51–3.32 (2H, m, CHC*H*$_2$OH), 2.95 (1H, dd, *J* = 14, 6.8 Hz, SO_2CH*H*CH), 2.58 (1H, s, O*H*), 2.39–2.19 (1H, m, CH_3CH), 1.08 (3H, d, *J* = 6.9 Hz, C*H*$_3$CH); *m*/*z* (EI): 196 (M^+-H_2O, 1), 184 (8), 172 (36), 156 (8), 143 (100), 142 (91), 132 (7), 125 (25), 107 (6), 94 (14), 78 (84), 77 (78), 55 (30); FT-IR (film) 3516, 1586, 1448, 1303, 1148, 1086, 1040, 742, 689 cm^{-1}. Anal. calcd for $C_{10}H_{14}O_3S$: C, 56.05; H, 6.59. Found: C, 56.13; H, 6.56%.

4.4. Oxidation of sulphide 6 to sulfone 7

4.4.1. Preparation of (*R*)-(−)-7[3a,4a] **from (*R*)-(−)-6**. A solution of alcohol (*R*)-(−)-**6** (3 g, 16.5 mmol, 90% e.e.) in CH_2Cl_2 (60 mL) was cooled to −78°C and treated under stirring with MCPBA (8.5 g of a 70% commercial reagent, 34 mmol). After 1 h the reaction was allowed to warm to room temperature and stirred for further 2 h. The MCBA was removed by filtration and the filtrate was washed in turn with saturated $NaHCO_3$ solution

(40 mL), and 5% aq. Na_2SO_3 (40 mL). The organic layer was concentrated under reduced pressure and the residue was purified by chromathography eluting with hexane–ethyl acetate (9:1→6:4) to afford pure (98% GC) (*R*)-(−)-**7** (3.2 g, 15 mmol, 91%): $[\alpha]_D^{20}=-8.5$ (*c* 1, $CHCl_3$); Ref. 3a $[\alpha]_D^{20}=-8.8$ (*c* 1.17, $CHCl_3$); analytical data identical to those above reported for (*S*)-(+)-**7**.

4.4.2. Preparation of (*S*)-(+)-7 from (*S*)-(+)-6. The alcohol (*S*)-(+)-**6** (4 g, 22 mmol, 65% e.e.) was oxidised using the same conditions described above to give pure (97% GC) (*S*)-(+)-**7** (4.32 g, 20.2 mmol, 92%): $[\alpha]_D^{20}=+6.2$ (*c* 1, $CHCl_3$); analytical data identical to those above reported for (*S*)-(+)-**7**.

4.5. Determination of the optical purity of compounds 6 and 7

4.5.1. Preparation of (±)-6 and (±)-7. A sample of (±)-**6** was prepared by base catalysed addition of thiophenol on methacrolein **8** using the same conditions described above in the preparation of acetal **14**. The obtained aldehyde was reduced with $NaBH_4$ to give the (±)-**6**. A sample of (±)-**7** was prepared by MCPBA oxidation of (±)-**6** using the same conditions for the preparation of (*R*)-(−)-**7** from (*R*)-(−)-**6**.

4.5.2. Preparation of the (*S*)-(−)-MTPA esters[11] of the samples of 6 and 7. *(Representative example).* A solution of (±)-**6** (20 mg, 0.11 mmol) in CCl_4 (0.4 mL) was treated with (*S*)-(−)-MTPACl[11] (30 mg, 0.12 mmol) and pyridine (0.2 mL) at room temperature for 24 h. The mixture was diluted with diethyl ether (40 mL) and washed in turn with 5% HCl aq. (50 mL) and saturated $NaHCO_3$ (10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residual (*S*)-(−)-MTPA ester was analysed without further purification.

The (*S*)-(−)-MTPA esters of (±)-**7** and of the different samples of enantioenriched **6** and **7** were prepared using the above described procedure. The NMR analysis of (*S*)-(−)-MTPA esters of (±)-**6** and (±)-**7** (250 MHz, $CDCl_3$) shows that the signal of methyl group became a well resolved double doublet:

(±)-**6**-(*S*)-(−)-MTPA esters: δ ppm: 1.04 and 1.06, $J=$ 6.8 Hz

(±)-**7**-(*S*)-(−)-MTPA esters: δ ppm: 1.10 and 1.14, $J=$ 6.8 Hz

The enantiomeric purity of all samples was determined by comparison of the area of the two peaks of these different doublets.

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