

Synthesis of 1,3-Dithianes and 1,3-Dithiolanes. Baker's Yeast Reduction and Lipase-Catalyzed Resolution for Synthesis of Enantiopure Derivatives

Thorleif Anthonsen,^{a,*} Bård H. Hoff,^a Nini U. Hofsløkken,^b Lars Skattebøl^{b,*} and Eirik Sundby^a

^aDepartment of Chemistry, Norwegian University of Science and Technology, N-7034 Trondheim, Norway and

^bDepartment of Chemistry, University of Oslo, PO Box 1033 Blindern, N-0315 Oslo, Norway

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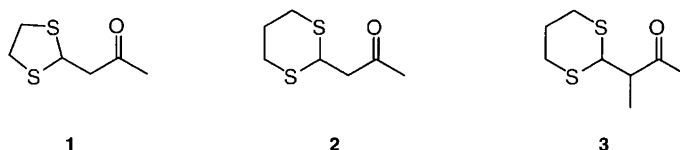
Three 1,3-dithiolanes and four 1,3-dithianes have been synthesised from 1-(1,3-dithiolan-2-yl)-2-propanone and 1-(1,3-dithian-2-yl)-2-propanone, respectively. Asymmetric reductions of these ketones using baker's yeast gave the corresponding enantiopure (*S*)-alcohols. Baker's yeast also reduced the double bond in 3-(1,3-dithian-2-yl)-3-buten-2-one enantioselectively to give (*S*)-3-(1,3-dithian-2-yl)-2-butanone. 3-(1,3-Dithian-2-yl)-3-buten-2-one was also reduced chemoselectively and the resulting 3-(1,3-dithian-2-yl)-3-buten-2-ol was resolved by transesterification in organic solvent using lipase B from *Candida antarctica* to yield the (*S*)-alcohol and the (*R*)-acetate with very high enantiomeric ratio, *E*. Racemic 1-(1,3-dithiolan-2-yl)-2-propanol and 1-(1,3-dithian-2-yl)-2-propanol were also resolved under similar conditions to give the (*S*)-alcohols and the corresponding (*R*)-acetates.

1,3-Related oxygen functions are common structural features in natural products. Thioacetals with a carbonyl group at the β -position such as **1** and **2**¹ are versatile building blocks for the syntheses of a variety of natural products such as nonactic acid,² (*S,S*)-(+)-grahamimycin A₁³ and L-digitoxose.⁴ Enantiopure thioacetals have been obtained both by asymmetric baker's yeast reductions and by resolution. Asymmetric reduction of 1-(1,3-dithian-2-yl)-2-propanone (**2**) to give enantiomerically enriched 1-(1,3-dithian-2-yl)-2-propanol with different microorganisms has been reported; baker's yeast gives predominantly the (*S*)-enantiomer⁵ whereas a *Streptomyces* sp.^{2,6} gives the (*R*)-enantiomer. 1-(1,3-Dithiolan-2-yl)-2-propanol (**12**) and 1-(1,3-dithian-2-yl)-2-propanol (**13**) have been resolved using lipases Amano P, Amano CES from *Pseudomonas* and *Chromobacterium viscosum* lipase.⁷ The enantiomeric excesses obtained were high (>95% ee).

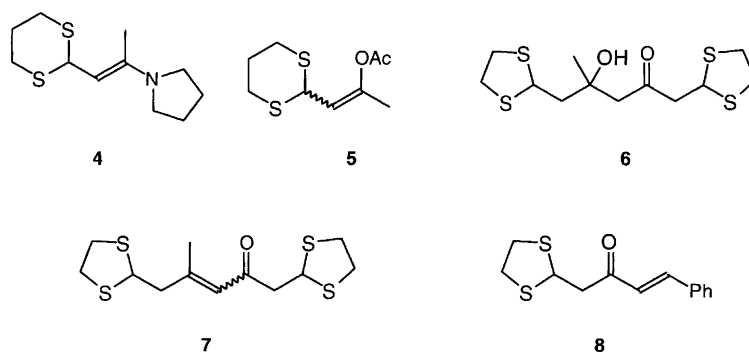
The thioacetals **1** and **2** have four chemically reactive carbon sites: the thioacetal carbon, the carbonyl carbon and the enolate carbon atoms. The present work is primarily aimed at selective reactions at the enolate carbons and subsequent enzyme-catalyzed transformation of the compounds thus obtained to give enantiopure derivatives.

Results and discussion

Non-enzymatic synthesis. The thioacetals **1** and **2** were prepared by transacetalization of commercially available 1,1-dimethoxy-2-propanone with 1,2-ethanedithiol and 1,3-propanedithiol, respectively. Using carbon tetrachloride as the solvent and trifluoroacetic acid as the catalyst the yield of **2** was considerably improved compared with that of previous procedures.¹ The thioacetal **3** was prepared as previously reported.⁸ Enolate reactions



* To whom correspondence should be addressed.

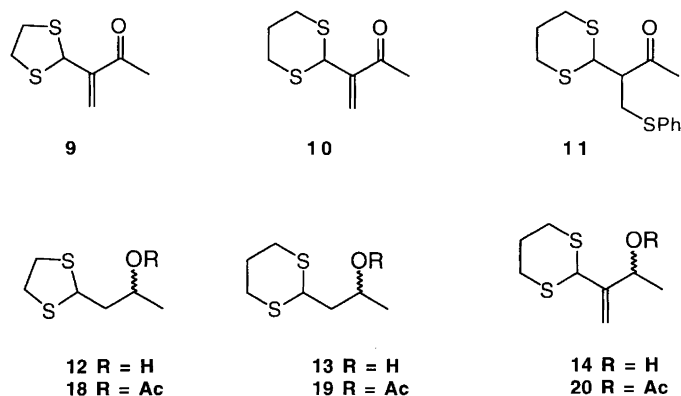


of the thioacetals have not been reported previously. Treatment of either acetal **1** or **2** with LDA followed by quenching with acid chlorides, allyl bromide or benzyl bromide resulted in dark colored complex product mixtures. The enamine **4** was obtained in 81% yield as a single isomer, presumably the *E*-isomer, in almost quantitative yield from the ketone **2** and pyrrolidine, but subsequent treatment with methyl iodide failed to give any *C*-alkylation. Employing anhydrous magnesium dichloride–triethylamine as base, the enolate reactions of **1** with acetyl chloride gave a 59% yield of the corresponding *O*-acylated products **5** as a mixture of stereoisomers, with no indication of any *C*-acylation having occurred. Similarly, with chlorotrimethylsilane only the *O*-silylated product was obtained.

We then turned to aldol reactions. Reaction of compound **1** in acetonitrile in the presence of magnesium dichloride–triethylamine at room temperature resulted in self-condensation to yield 63% of the β -hydroxy ketone **6** and 21% of an inseparable mixture of isomeric alkenes **7**. By extending the reaction time, more of the alkenes were formed as expected, but the aldol **6** was surprisingly stable towards elimination under the reaction conditions. Using the same base system the thioacetal **1** in acetonitrile reacted with benzaldehyde at room temperature affording the enone **8**, with (*E*)-configuration ($J_{trans} = 16$ Hz), in 58% yield and none of the self-condensation products **6** and **7**. The enone **8** was also the product from the same reaction using LDA as the base, but the yield was only 10%. Condensations of the thioacetals with paraformal-

dehyde took place as well, albeit in low yields. The best conditions were found to be heating the reactants in isobutyronitrile under reflux for several hours. Under these conditions the reaction of **1** afforded 16% yield of **9** while, from **2**, a 36% yield of **10** was obtained. The enones were the only products and in both cases the condensation took place at the internal carbon of the thioacetal. The products are probably the result of thermodynamic control of the reaction, promoted by the high temperature and long reaction time. Without isolation of the enone **10**, thiophenol was added to the reaction mixture to furnish the Michael addition product **11** in 25% yield.

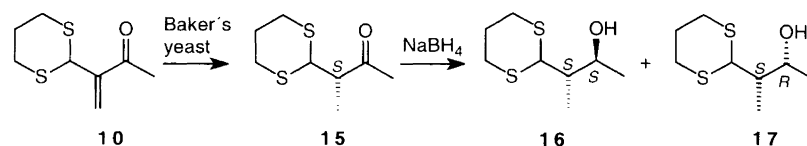
Baker's yeast reductions. The thioacetals 1-(1,3-dithiolan-2-yl)-2-propanone (**1**) and 1-(1,3-dithian-2-yl)-2-propanone (**2**) were reduced with baker's yeast to yield the corresponding (*S*)-alcohols [(*S*)-**12** and (*S*)-**13** respectively] on a gram scale with very high ee (ee > 99%). The enone **10** was reduced by baker's yeast to yield an enantiopure ketone (**15**) (chiral GLC), however, of unknown configuration (see Scheme 1). This type of reaction has been described previously.⁹ The keto group was further reduced with NaBH₄ to give a mixture of diastereomers (**16** and **17**). The optical rotation of this mixture was $[\alpha]_D^{20} = +15^\circ$. The *syn*(–) and *anti*(+) forms of 3-(1,3-dithian-2-yl)-2-butanol have been prepared previously and their absolute configurations have been determined as (2*S*,3*R*) and (2*S*,3*S*), respectively.¹⁰ The optical rotations of the *syn*(–) form was -21° and of the



12 R = H
18 R = Ac

13 R = H
19 R = Ac

14 R = H
20 R = Ac



Scheme 1.

anti(+) form $+24^\circ$. The two unknown stereoisomers, *syn*(+) ($2R,3S$) and *anti*(-) ($2R,3R$) would be expected to have optical rotations of $+21$ and -24 , respectively. Since it is evident that the ($3R$)-diastereomers are levorotatory while those with ($3S$)-configuration are dextrorotatory, the stereochemistry of **15** had to be ($3S$) as shown in Scheme 1.

Lipase-catalyzed resolutions. Sodium borohydride reduction of **1**, **2** and the enone **10**, the last in the presence of cesium chloride, gave chemoselective reduction of the keto groups to yield racemates **12**, **13** and **14** respectively. The racemic mixtures were resolved by transesterification in organic solvent using lipase B from *Candida antarctica* (CALB) as the catalyst. The solvent of choice for such reactions is hexane, however owing to low solubility *tert*-butyl methyl ether was used for the resolution of **14**.

The success of a kinetic resolution depends on the relative reactivity of the two enantiomers, which is expressed by the enantiomeric ratio E .¹¹ However, since the reactions described in the present work take place in an organic solvent, the equilibrium of the reaction (acyl donor + racemic alcohol = formed ester + leaving alcohol) is also a crucial factor to be considered. For the resolution of **12**, **13** and **14** ethyl acetate, vinyl acetate and acetic anhydride were used as acyl donors. When ethyl acetate was used in hexane the low K_{eq} -value led to non-optimal ee -values owing to reversible reaction. However, when the reaction was performed in ethyl acetate solution the E -values obtained were excellent ($E > 300$). Vinyl acetate as the acyl donor also gave similar results (see the Experimental part). The configuration of the formed esters as (R) and hence the unreacted alcohols as (S) may be concluded from knowledge of the stereopreference of the lipase catalyst. There are numerous examples of resolutions of secondary alcohols catalyzed by CALB.^{12–16} Owing to the geometry of the active site of the enzyme, the relative reaction rate of the enantiomers will be governed primarily by the size of the ‘small’ (for **12**, **13** and **14** methyl) and ‘large’ (thioacetal moiety) group at the stereocenter. Moreover, the configurations of **12** and **13** agree with the results from the baker’s yeast reductions and their optical rotations with earlier reports.^{5,7} Furthermore, the enantiomeric ratio, E , was very high for all resolutions, well above 300, which means that the (R)-form is acylated 300 times faster than the (S)-form and thus confirms that these substrates are excellently suited for resolution by CALB. The two enantiomers of **14** had the same relative order of elution from the chiral column as substrates **12**, **13**

and other secondary alcohols recently investigated.^{12,14} All of the three alcohols (S)-**12**, (S)-**13** and (S)-**14** and acetates (R)-**18**, (R)-**19** and (R)-**20** were isolated. When acetic anhydride was used as the acyl donor lower E -values, due to non-enzymatic esterification, were observed. Esterification of **13** with acetic acid was also attempted; the E -value was high, but the reaction had a low equilibrium constant (K_{eq}).

The resolutions described proceeded at a high rate in hexane. A conversion of 50% was reached within 7 h and as a consequence of the high E -values, the degree of conversion did not increase significantly after 7 days. The choice of acylating agent is important. If the produced ester is the required enantiomer, ethyl acetate may be used. When ethyl acetate is used as both acyl donor and solvent, the reaction stops before 50% conversion and the product enantiomer can be collected enantiomerically pure in high yield. Careful monitoring of the reaction is not necessary. The drawback is that the reaction is slow compared with reactions in hexane. If the substrate is the required enantiomer vinyl acetate or vinyl butanoate should be used. Then the reaction goes to completion, but, owing to the high E -values in these reactions, the rate of reaction after 50% conversion is so slow that terminating the reaction at the right moment is simple. Successful preparative resolutions were performed with vinyl acetate as the acyl donor, and both enantiomers were prepared with 98–99% ee without monitoring the reactions.

Experimental

General. Immobilized CALB (Novozyme 435, Novo-Nordisk A/S) had an activity of 7000 PLU g^{-1} , and a water content of 1–2% w/w. Dried *Saccharomyces cerevisiae* was a gift from Idun Industri, Oslo batch No. 102, 1.4.98. Solvents were dried over molecular sieves.

Optical rotations were determined using an Optical Activity Ltd. AA-10 automatic polarimeter, concentrations are given in g/100 ml.

Chiral analyses were performed using Varian 3300 and 3400 gas chromatographs equipped with CP-Chiracil-DEX-CB columns from Chrompack (25 m; 0.25 mm, 0.25 or 0.32 μm film density). For GLC details see Ref. 17.

NMR spectroscopy was performed for samples in $CDCl_3$ solutions, unless otherwise stated, using Varian 200 and Bruker DPX 300 and 400 instruments, operating at 200, 300 and 400 MHz for 1H and 50, 75 and 100 MHz for ^{13}C . Chemical shifts are in ppm relative to tetra-

methylsilane. COSY experiments were used for assignments.

Transesterifications, small scale. The substrate (1.31×10^{-4} mol) was added to the solvent (3 ml). For reactions where EtOAc was not the solvent, vinyl acetate (vinylOAc) (6.55×10^{-4} mol) was added. The reactions were started by adding CALB (20 mg for reactions with EtOAc and 10 mg for reactions with vinylOAc) to the reaction mixtures. The reactions were performed in a shaker incubator at 30 °C. For substrates **12** and **13** chiral GLC analysis gave ee_s - and ee_p -values from which conversion, c , was calculated, $c = ee_s / (ee_s + ee_p)$. For substrate **14** conversion was measured using *n*-hexadecane as an internal standard. In control experiments without enzyme, no acylation was observed using either vinylOAc or EtOAc as acyl donor. Enantiomer ratios, E and equilibrium constants, K_{eq} were calculated using the computer program E and K Calculator Version 2.03.¹⁸ Results: **12** EtOAc and vinylOAc, $E=400$; **13** EtOAc, $E=520$, vinylOAc, $E=330$; **14**, EtOAc and vinylOAc, $E>300$.

1-(1,3-Dithiolan-2-yl)-2-propanone (1) and 1-(1,3-dithian-2-yl)-2-propanone (2) were prepared by transacetalization of commercially available 1,1-dimethoxy-2-propanone with 1,2-ethanedithiol and 1,3-propanedithiol, respectively.¹ By use of CCl_4 as the solvent and trifluoroacetic acid as the catalyst the yield of **2** was considerably improved compared with that of previous procedures.

3-(1,3-Dithian-2-yl)-2-butanone (3) was prepared as previously reported.⁸

Baker's yeast catalyzed reduction of ketones 1 and 2. The medium consisted of sucrose (16 g), dry baker's yeast (5 g) and 100 ml phosphate buffer (pH 7.4, 0.1 M) and the reductions were carried out at 25 °C. The cultures were pre-incubated for 30 min before the substrates (50 mg, dissolved in 1 ml EtOH) were added and the incubation was continued under the same conditions. Progress of the reaction was monitored by TLC. Preparative transformations were performed by a scale-up of the screening procedure. Ketones **1** (9.5 g in 2.0 l medium) and **2** (200 mg in 200 ml medium) were reduced as described. The incubation medium was filtered through Celite, saturated with NaCl and filtered again. EtOAc was used for repeated extractions, the combined organic phases were dried ($MgSO_4$) and evaporated using a rotary evaporator. The crude products were purified by column chromatography (EtOAc–acetone, 8:2) to give (*S*)-1-(1,3-dithiolan-2-yl)-2-propanol [(*S*)-**12**] (6.5 g, 69%) and (*S*)-1-(1,3-dithian-2-yl)-2-propanol [(*S*)-**13**] (86 mg, 43%), respectively, both with $ee > 99$. Optical rotations corresponded well with previous⁵ and own values (see below).

1-(1,3-Dithian-2-yl)-2-pyrrolidin-1-yl-1-propene (4). Pyrrolidine (0.546 g, 7.68 mmol) was added to a solution of

the thioacetal **2** (0.504 g, 2.86 mmol) in benzene (15 ml) and heated under reflux for 42 h, while water was removed by means of a Dean–Stark trap. Evaporation gave 650 mg (99%) of **4** as a dark yellow liquid. ¹H NMR (200 MHz, CD_2Cl_2): δ 1.62–1.78 (m, 4 H), 1.81–1.88 (m, 4 H), 1.94 (s, 3 H), 1.99–2.12 (m, 1 H), 2.66–3.02 (m, 4 H), 3.06–3.13 (m, 4 H), 3.71 (d, J 10.1 Hz, 1 H), 4.87 (d, J 10.1 Hz, 1 H). ¹³C NMR (50 MHz, acetonitrile – d_3): δ 15.8, 25.0, 25.8, 32.05, 46.4, 48.1, 91.4, 107.9. IR (film): 1616 cm^{-1} .

2-Acetoxy-1-(1,3-dithian-2-yl)-1-propene (5). Acetyl chloride (0.243 g, 3.10 mmol) in THF (10 ml) was added to a mixture of $MgCl_2$ (0.300 g, 3.15 mmol), triethylamine (0.670 g, 6.62 mmol) and the thioacetal **2** (0.487 g, 2.76 mmol) in THF (15 ml) at room temp. The mixture was stirred at room temp. for 18 h after which the usual work-up and purification by flash chromatography (silica gel; CH_2Cl_2 –pet. ether 7:3) gave 0.289 g of recovered **2** and 0.0147 g (59%) of **5** as a 4:1 mixture of *Z*:*E* isomers, respectively. *Z*-isomer: ¹H NMR (200 MHz): δ 1.71–1.90 (m, 1 H), 1.92 (d, J 1.0 Hz, 3 H), 1.99–2.07 (m, 1 H), 2.17 (s, 3 H), 2.70–3.00 (m, 4 H), 4.79 (d, J 10 Hz, 1 H), 5.04–5.12 (m, 1 H). *E*-isomer ¹H NMR (200 MHz): δ 1.71–1.90 (m, 1 H), 1.97 (d, J 1.0 Hz, 3 H), 1.99–2.07 (m, 1 H), 2.08 (s, 3 H), 2.70–3.00 (m, 4 H), 4.73 (d, J 10 Hz, 1 H), 5.15–5.23 (m, 1 H). ¹³C NMR for the mixture of the *Z*:*E* isomers (50 MHz): δ 19.5, 20.9, 24.7, 24.8, 29.9, 30.2, 40.7, 42.7, 113.7, 114.9, 148.2, 168.3. IR (film): 2880, 1745, 1680, 1420, 1360, 1270, 1220, 1180, 1010, 1000 cm^{-1} . MS (EI): m/z 218 (M^+), 175, 159, 101, 43 (100). Anal. (HRMS). Found: 218.043353; calc. for $C_9H_{14}O_2S_2$: 218.043523.

1,5-Bis-(1,3-dithiolan-2-yl)-4-hydroxy-4-methyl-2-pentanone (6). A solution of triethylamine (1.44 g, 14.26 mmol), $MgCl_2$ (0.646 g, 6.78 mmol), and **1** (1.00 g, 6.16 mmol) in acetonitrile (15 ml) was stirred at room temp. for 15 h. The usual work-up and purification by flash chromatography (silica gel; CH_2Cl_2) gave 0.174 g of recovered **1**, 21% of a mixture of isomeric alkenes **7** and 0.518 g (63%) of the aldol (**6**) as a yellow liquid. ¹H NMR (200 MHz): δ 1.22 (s, 3 H), 2.07–2.12 (m, 2 H), 2.49–2.73 (m, 2 H), 2.97–3.27 (m, 6 H), 3.70 (s, 1 H), 4.55 (t, J 6.7 Hz, 1 H), 4.75 (t, J 7.0 Hz, 1 H). ¹³C NMR (50 MHz): δ 26.9, 38.2, 46.1, 48.1, 49.3, 51.8, 53.9, 71.0, 208.8. IR (film): 3450, 2940, 2900, 1690, 1360 cm^{-1} . MS (EI): m/z 306 ($M^+ - H_2O$), 162, 147, 105, 43 (100). Anal. (HRMS). Found: 306.022553; calc. for $C_{12}H_{18}OS_4$: 306.024053.

1-(1,3-Dithiolan-2-yl)-4-phenyl-3-buten-2-one (8). A solution of triethylamine (0.381 g, 3.77 mmol), $MgCl_2$ (0.171 g, 1.80 mmol), benzaldehyde (0.252 g, 2.37 mmol) and **1** (0.250 g, 1.54 mmol) in acetonitrile (15 ml) was stirred at room temp. for 16 h. The usual work-up and purification by flash chromatography (silica gel; CH_2Cl_2 –pet. ether 9:1) furnished 0.044 g (0.271 mmol)

of recovered **1** and 0.185 g (58%) of **8** as an orange sticky solid, m.p. 78–83 °C. ¹H NMR (200 MHz): δ 3.16–3.27 (m, 6 H), 4.93 (t, *J* 7.0 Hz, 1 H), 6.70 (d, *J* 16 Hz, 1 H), 7.35–7.58 (m, 6 H). ¹³C NMR (50 MHz): δ 38.4, 38.6, 125.4, 126.8, 128.2, 128.5, 128.8, 130.5, 134.0, 143.2, 197.0. IR (film): 1675, 1650, 1605, 1440, 1415, 1380, 1345 cm⁻¹. GC–MS (EI): *m/z* 250 (*M*⁺), 222, 189, 146, 131 (100), 103. Anal. (HRMS). Found: 250.050517; calc. for C₁₃H₁₄OS₂: 250.048609.

3-(1,3-Dithiolan-2-yl)-3-buten-2-one (9). A solution of MgCl₂ (0.574 g, 6.03 mmol), Et₃N (1.523 g, 15.05 mmol), paraformaldehyde (0.807 g, 26.9 mmol) and **1** (0.650 g, 4.01 mmol) in isobutyronitrile (30 ml) was heated under reflux for 2 h. The usual work-up and purification by flash chromatography (silica gel; CH₂Cl₂) furnished 0.099 g of recovered **1** and 0.097 g (16%) of the enone **9** as a liquid. ¹H NMR (200 MHz): δ 2.35 (s, 3 H), 3.07–3.27 (m, 4 H), 5.44 (s, 1 H), 6.13 (s, 1 H), 6.32 (s, 1 H). ¹³C NMR (50 MHz): δ 26.7, 38.4, 49.7, 125.0, 147.8, 197.5. IR (film): 2925, 2855, 1709, 1652, 1567, 1419, 1359, 1329 cm⁻¹.

3-(1,3-Dithian-2-yl)-3-buten-2-one (10). A solution of diisopropylethylamine (4.24 g, 32.8 mmol), MgCl₂ (1.49 g, 15.7 mmol), paraformaldehyde (4.55 g, 152 mmol) and **1** (2.50 g, 14.20 mmol) in isobutyronitrile (60 ml) was heated under reflux for 2 h at which time further paraformaldehyde (4.67 g, 156 mmol) was added. After 16 h reflux the usual work-up and purification by flash chromatography (silica gel; benzene–EtOAc, 95:5) afforded 0.101 g of recovered **1** and 0.775 g (36%) of the enone **10** as a liquid. ¹H NMR (200 MHz): δ 1.70–1.93 (m, 1 H), 2.03–2.19 (m, 1 H), 2.34 (s, 3 H), 2.75–3.09 (m, 4 H), 5.24 (s, 1 H), 6.30 (d, *J* 4.7 Hz, 2 H). ¹³C NMR (50 MHz): δ 25.2, 25.5, 31.9, 129.5, 146.9, 196.0. IR (film): 2920, 2890, 1670, 1610, 1410, 1355, 1315, 1270, 1235, 1210, 1100 cm⁻¹. MS (EI): *m/z* 188 (*M*⁺), 173, 43 (100). Anal. (HRMS). Found: 188.032456; calc. for C₈H₁₂OS₂: 188.032959.

3-(1,3-Dithian-2-yl)-4-phenylthio-2-butanone (11). A solution of triethylamine (1.99 g, 19.7 mmol) MgCl₂ (0.903 g, 9.48 mmol), paraformaldehyde (2.50 g, 83.2 mmol) and **2** (1.50 g, 8.49 mmol) in THF (25 ml) was heated for 2 h after which time further paraformaldehyde (2.54 g, 84.5 mmol) was added. After being refluxed for 16 h the reaction mixture was cooled to room temp. and thiophenol (0.98 ml, 9.54 mmol) was added. Stirring was continued for 3 h at room temp. after which the usual work-up and purification by flash chromatography (silica gel; CH₂Cl₂–pet. ether 8:2) furnished 0.126 g of recovered **2** and 0.171 g (25%) of **11** as a white solid, m.p. 72–75 °C. ¹H NMR (200 MHz): δ 1.75–2.12 (m, 2 H), 2.27 (s, 3 H), 2.77–2.84 (m, 4 H), 3.02–3.28 (m, 2 H), 3.50 (dd, *J* 12.7, 2.8 Hz, 1 H), 4.11 (d, *J* 10 Hz, 1 H), 7.15–7.50 (m, 5 H). ¹³C NMR (50 MHz): δ 25.2, 28.7, 28.9, 32.4, 33.3, 46.6, 54.4, 126.1,

128.7, 129.1, 134.6, 206.9. IR (film): 2920, 2880, 1705, 1570, 1470, 1430, 1410, 1345 cm⁻¹. MS (EI): *m/z* 298 (*M*⁺), 255, 188, 175, 145, 119 (100). Anal. (HRMS). Found: 298.052451; calc. for C₁₂H₁₈OS₃: 298.051981.

rac-1-(1,3-Dithiolan-2-yl)-2-propanol (12) and rac-1-(1,3-dithian-2-yl)-2-propanol (13) were synthesized from the corresponding ketones **1** and **2** by NaBH₄ reduction under standard conditions. **12**: ¹H NMR (400 MHz): δ 1.24 (d, *J* 6.4, 3 H), 1.88–2.05 (m, 2 H), 3.19–3.32 (m, 4 H), 3.94–4.02 (m, 1 H) and 4.69 (dd, *J* 8.1, 8.1 Hz, 1 H). (See also Ref. 7). ¹³C NMR (100 MHz): δ 24.2, 38.6, 38.8, 48.1, 50.9, 67.8. GC–MS (EI): *m/z* 166 (*M*⁺ + 2), 164 (*M*⁺), 146, 131, 105 (100), 61. **13**: ¹H NMR (300 MHz): δ 1.23 (d, *J* 7.1 Hz, 3 H), 1.76–1.95 (m, 3 H), 2.05–2.21 (m, 1 H), 2.77–2.97 (m, 1 H), 4.03–4.18 (m, 1 H), 4.24 (dd, *J* 5.7, 8.0 Hz, 1 H). (See also Ref. 5). ¹³C NMR (75 MHz): δ 23.9, 26.3, 30.5, 30.7, 44.7, 44.8, 66.3. GC–MS (EI): *m/z* 180 (*M*⁺ + 2), 178 (*M*⁺), 145, 119, 74, 59, 45 (100).

rac-3-(1,3-Dithian-2-yl)-3-butene-2-ol (14). A mixture of 3-(1,3-dithian-2-yl)-3-buten-2-one (**10**) (1.2 g, 6.4 mmol) and CeCl₃·7H₂O (1 equivalent) in MeOH (55 ml) was cooled to 0 °C and NaBH₄ (1 equivalent) was added. The reaction mixture was stirred for 5 min and dilute HCl was added. The reaction mixture was extracted with Et₂O and the crude product was filtered through a short silica column, yield 1.10 g (90%). ¹H NMR (400 MHz): δ 1.37 (d, *J* 6.4 Hz, 3 H), 1.81 (OH), 1.82–1.95 (m, 1 H), 2.11–2.18 (m, 1 H), 2.84–2.89 (m, 2 H), 2.95–3.05 (m, 2 H), 4.44 (q, *J* 6.4 Hz, 1 H), 4.67 (s, 1 H), 5.47 (s, 1 H), 5.37 (s, 1 H). ¹³C NMR (100 MHz): δ 22.8, 25.7, 32.6 (2C), 47.4, 70.4, 115.6 and 151.6. GC–MS (EI): *m/z* 192 (*M*⁺ + 2), 190 (*M*⁺), 172 (100), 119, 106, 101, 97.

Transesterifications, preparative scale of 12–14 using vinyl acetate as the acyl donor. The substrate (**12**, 1.77 g; **13**, 1.03 g; **14**, 0.78 g) and vinylOAc (five-molar excess) was suspended in the solvent (40 ml) and immobilized CALB (100 mg) was added. The reaction was left for 18 h in a shaker at room temp. The enzyme was filtered off, and the solvent and acyl donor were removed at reduced pressure. The alcohol and ester were separated by column chromatography (CH₂Cl₂–pet. ether–acetone 6:3:1).

(S)-1-(1,3-Dithiolan-2-yl)-2-propanol [(S)-12], isolated 0.71 g (40%), ee > 99, [α]_D²⁰ = +27.3 (*c* 1.1, CHCl₃).

(R)-2-Acetoxy-1-(1,3-dithiolan-2-yl)propane [(R)-18], isolated 1.00 g (45%), ee = 98, [α]_D²⁰ = –11.0 (*c* 1.0, CHCl₃). ¹H NMR (400 MHz): δ 1.26 (d, *J* 6.2 Hz, 3 H), 2.06 (s, 3 H), 1.94–2.01 (m, 1 H), 2.14–2.22 (m, 1 H), 2.80–2.93 (m, 4 H), 4.05 (dd, *J* 8.5, 8.5 Hz, 1 H), 4.98–5.06 (m, 1 H). (See also Ref. 7). ¹³C NMR (100 MHz): δ 20.6, 21.7, 38.5, 39.0, 45.8, 50.0, 70.5, 170.8. GC–MS (EI): *m/z* 146, 131, 105, 85, 43 (100).

(*S*)-1-(1,3-dithian-2-yl)-2-propanol [(*S*)-**13**], isolated 0.44 g (43%), ee > 99. $[\alpha]_{\text{D}}^{20} = +25.5$ (*c* 1, CHCl₃).

(*R*)-2-Acetoxy-1-(1,3-dithian-2-yl)propane [(*R*)-**19**], isolated 0.60 g (47%), ee > 98, $[\alpha]_{\text{D}}^{20} = +7.6$ (*c* 1, CHCl₃). ¹H NMR (300 MHz): δ 1.25 (d, *J* 6.2 Hz, 3 H), 2.05 (s, 3 H), 1.83–1.94 (m, 2 H), 2.02–2.17 (m, 2 H), 2.78–2.94 (m, 4 H), 4.05 (dd, *J* 8.6, 8.6 Hz, 1 H), 5.09–5.20 (m, 1 H). (See also Ref. 7). ¹³C NMR (75 MHz): δ 20.6, 21.7, 26.1, 30.3, 30.5, 41.8, 43.8, 68.3, 170.7. GC-MS (EI): *m/z* 220 (*M*⁺), 160, 145, 119, 85, 43 (100).

(*S*)-3-(1,3-Dithian-2-yl)-3-buten-2-ol [(*S*)-**14**], isolated 0.33 g (42%), ee > 99, $[\alpha]_{\text{D}}^{20} = -15.3$ (*c* 1.5, CHCl₃).

(*R*)-3-Acetoxy-2-(1,3-dithian-2-yl)-1-butene [(*R*)-**20**], isolated 0.45 g (47%), ee > 98 (determined after reductive removal of the acetyl group), $[\alpha]_{\text{D}}^{20} = +54.0$ (*c* 1.5, CHCl₃). ¹H NMR (400 MHz): δ 1.44 (d, *J* 6.6 Hz, 3 H), 2.10 (s, 3 H), 1.85–1.97 (m, 1 H), 2.11–2.19 (m, 1 H), 2.85–3.04 (m, 4 H), 4.58 (s, 1 H), 5.45 (q, *J* 6.6 Hz, 1 H), 5.43 (s, 1 H), 5.57 (s, 1 H). ¹³C NMR (100 MHz): δ 20.3, 21.7, 25.7, 32.3 (2 C), 47.9, 71.7, 117.2, 147.6, 170.4. GC-MS (EI): *m/z* 232, 172 (100), 144, 139, 125, 97.

(*R*)-3-(1,3-Dithian-2-yl)-3-buten-2-ol [(*R*)-**14**]. The acetate (*R*)-**20** (165 mg) was hydrolyzed in phosphate buffer (pH 7.0, 0.1 M), using CALB as the catalyst, to yield (*R*)-**14**, 130 mg (96%), $[\alpha]_{\text{D}}^{20} = +16.0$ (*c* 1.0, CHCl₃).

Transesterifications, preparative scale, of 13 in ethyl acetate. Immobilized CALB (100 mg) was added to **13** (460 mg) in EtOAc (40 ml). The reaction was left for 18 h in a shaker. The enzyme was filtered off and the solvent removed. The alcohol and ester were separated by column chromatography (CH₂Cl₂-pet. ether-acetone 6:3:1), yielding (*S*)-**13**, 200 mg (43%), ee = 70%, and (*R*)-**19**, 185 mg (32%), ee > 99.

(*S*)-3-(1,3-Dithian-2-yl)-2-butanone (**15**). Preparative asymmetric reduction of **10** using baker's yeast gave **15** with modest enantiomeric excess (ee = 87%) within 24 h. By slow addition of **10** (200 mg in 2 ml EtOH) in small aliquots to a fermenting culture of baker's yeast over a 10 h period, this was raised to ee > 99%. Work-up and purification as described above gave 69 mg (34%) of **15**,

$[\alpha]_{\text{D}}^{20} = -10.2$ (*c* 0.78, CHCl₃). Ketone **15** was reduced by NaBH₄ in EtOH in the usual manner. The reaction was quenched by addition of 1% HCl to give a mixture of diastereomeric alcohols **16** and **17**, $[\alpha]_{\text{D}}^{20} = +15.0$ (*c* 1.2, CHCl₃).

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