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Stereoselective Reduction of Thiocarbonyl Compounds with Baker's Yeast

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Abstract: Alkyl esters of 3-thioxo-butanoic, -pentanoic and -hexanoic acid, 2-thioxo-1-cyclopentanecarboxylic acid ethyl ester, and 2-octanethione have been reduced with baker's yeast to give optically active thiols. The reductions parallel those of the oxygen analogues with respect to rate and diastereo- and enantioselectivity but, generally, the enantiomeric excess (ee) values are smaller. The influence of experimental variables such as substrate concentration, physiological condition of the yeast (resting/fermenting, fresh/dry/frozen), substrate modification, and addition of inhibitors on stereoselectivity has been studied. The formation of S-products was favoured by small substrate concentrations, use of dry or frozen yeast, and by addition of R-enzyme inhibitors (ethyl acrylate and biacetyl). The yields of thiol products are limited by extensive hydrolysis of the thioxo groups of all substrates used. In order to make meaningful comparisons of enantiomeric preferences in baker's yeast reduction of different substrates it is suggested that the maximum ee values reached below certain (substrate dependent) substrate/yeast ratios are used.

INTRODUCTION

To the best of our knowledge enzymic or microbial reduction of thioxo groups has not been investigated since the work of Neuberg and Nord regarding baker's yeast reduction of thioacetaldehyde to ethanethiol.[2] Baker's yeast catalysed oxidation of thiols to disulfides[3] and hydrolysis of a carbothioamide functionality to the oxygen analogue[4] are other known transformations involving thiol and thioxo groups. We now present our results of baker's yeast reductions of some β-thioxo esters and of 2-octanethione to give optically active thiols. Such thiols have attracted limited interest, but a number of synthetic procedures has appeared, most of them involving conversion of optically active alcohols to thiols, with inversion of configuration.[5] Important biological thiols are primary, dihydrolipoic acid being an exception, and the biological redox chemistry of thiols relates to the thiol-disulfide rather than to the thiol-thione system.

The thiocarbonyl compounds used in this work, **1a-e**, **4** and **7**, were prepared from the oxygen analogues by HCl catalysed reaction with H_2S.[6,7,8] Octane-2-thione, **7**, has not been described previously. The β-thioxo esters are known to be almost completely enethiolised, containing just enough of the thioxo-form to give them a weak reddish colour.[6] This raises the question whether the enzymic reduction actually proceeds as a reduction of the C-C double bond of the enethiol-form. Since the reduction, with respect to rate and enantioselectivity, parallels that of the oxygen counterparts it probably proceeds in the same way.

Unfortunately, the question has not yet been answered in the case of the otherwise well-investigated baker's yeast reduction of β-keto esters.[9]

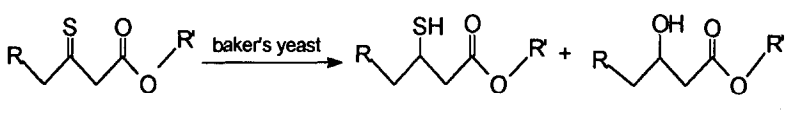
The mercapto compounds encountered in this work have not been previously described, except for the methyl ester **2b** and 2-octanethiol, **8**. Griesbeck and Seebach have prepared (R)-3-mercaptobutanoic acid.[10]

RESULTS AND DISCUSSION

When incubated with baker's yeast in water suspension β-thioxo esters **1** were transformed into mixtures of optically active β-mercapto esters **2**, and β-hydroxy esters **3**, Scheme 1. Since thiocarbonyl compounds are known to undergo rapid hydrolysis, the alcohol products clearly arise from reduction of the hydrolysis products. Unfortunately, the rate of hydrolysis is high enough to severely limit the chemical yields of thiols in preparative scale experiments. Small amounts of α,β-unsaturated esters and disulfides were detected by GC analyses of the product mixtures. The enantiomeric compositions of the thiols were easily determined by GC analysis of the diastereomeric thiocarbamates obtained upon reaction with (R)-1-phenylethyl isocyanate. As with the oxygen analogues the derivatives of the S-enantiomers elute first. The configurations of **2a,d,e** were established by transforming (S)-**3a** to (R)-**2a**, and (R)-**3d,e** to (S)-**2d,e** in Mitsunobu-Volante processes.[11] The methyl and butyl esters, **2b** and **2c**, were transesterified to **2a**.

The Table shows the results of a number of experiments reflecting the influence of parameters such as substrate concentration, physiological condition of the yeast (resting/fermentering, fresh/dry/frozen), substrate modification, and inhibitors on yield and enantiomeric purity of the thiol products. The experiments were carried out as follows: to a stirred suspension of 25 g of ordinary baker's yeast (compressed yeast, purchased in local shops) in 125 ml of tap water at room temperature was added inhibitor (if any), 25 g of sugar (in case of fermenting yeast) and, after 30 min, the substrate, either neat or dissolved in 50 ml of hexane; after 24 h, the hexane phase was separated by centrifugation and analysed. In experiments with no organic phase the suspension was extracted with CH_2Cl_2. Reliable product distribution values were obtained by CH_2Cl_2-extraction only, because hexane is too little polar to extract the alcohols **3** (an advantageous circumstance with respect to product purification in preparative experiments).

Scheme 1



1a-e **2a-e** **3a-e**

	R	R'
a	H	Et
b	H	Me
c	H	Bu
d	Me	Et
e	Et	Et

Comparison of exp.s 1 and 2 shows that fermenting yeast reduces faster than resting yeast, thereby favouring formation of thiol over alcohol product. The enantiomeric excess is not affected. By increasing the amount of substrate, exp.s 3-5, the relative yield of thiol product decreases, reflecting a higher degree of hydrolysis of the thioxo substrate. More importantly, the ee value also decreases markedly. This behaviour, also observed in baker's yeast reduction of the oxygen analogue where a high ee value (~ 98%, S) is obtained by adding small amounts of substrate or by adding larger amounts slowly,[12,13] may be interpreted in terms of rate-concentration curve differences for the S- and R-enzymes, inasmuch as the lack of total stereoselectivity in whole cell reductions usually is explained by the simultaneous operation of R- and S-enzymes. Isolated baker's

Table. Baker's yeast reductions of β-thioxo esters **1a-e** (see text).

exp.#	substr.	mmol	sugar	org.phase	inhibitor (ml)	thiol/alcohol (remarks)	ee(%) thiol[1)]
1	**a**	0.5	–	–	–	32/68	78
2	**a**	0.5	+	–	–	77/23	79
3	**a**	1.25	+	–	–	64/36	58
4	**a**	2.5	+	–	–	60/40	49
5	**a**	5.0	+	–	–	56/43	38
6	**a**	0.5	–	+	–	2)	78
7	**a**	0.5	+	+	–	2)	75
8	**a**	1.25	+	+	–	2)	76
9	**a**	2.5	+	+	–	2)	78
10	**a**	0.034	+	+	–		81
11	**b**	0.5	–	+	–		80
12	**c**	0.5	–	+	–		76
13	**a**	0.5	–	+	–	dry yeast	87
14	**a**	0.5	+	+	–	dry yeast	89
15	**a**	0.5	–	+	–	frozen yeast	87
16	**a**	0.5	–	+	ethyl acetoacetate (1)		5
17	**a**	0.5	–	+	allyl alcohol (0.005)		87
18	**a**	0.5	–	+	allyl alcohol (0.025)		89
19	**a**	0.5	–	+	allyl alcohol (0.175)		66
20	**a**	0.5	–	+	ethyl acrylate (1)		90
21	**a**	0.5, 2.5	–	+	biacetyl (1)		93
22	**a**	2.5	+	+	ethyl acrylate (1)+biacetyl (1)		93
23	**a**	0.5	–	+	ethyl acrylate (1)	dry yeast	92
24	**d**	0.5	+	–	–		41
25	**d**	0.5	–	+	–	3)	30
26	**d**	0.5	+	+	–	2)	56
27	**d**	2.5	+	+	–	2)	57
28	**d**	0.5	+	+	ethyl acrylate (1)		80
29	**e**	0.5	+	–	–		40(R)
30	**e**	0.5	–	+	–	4)	2.8
31	**e**	0.5	+	+	–	5)	1.6
32	**e**	2.5	+	+	–	6)	0.8
33	**e**	0.5	+	+	ethyl acrylate (1)		32
34	**e**	0.5	+	–	biacetyl (1)		73(R)

[1)] S-configuration unless otherwise stated, [2)] small amounts of substrate not converted, [3)] 42% substrate conversion. [4)] 30% substrate conversion, [5)] 60% substrate conversion, [6)] 50% substrate conversion

yeast enzymes have been shown to be highly stereoselective in reduction of β-keto esters.[14-16] The hardly significant improvement of the ee value (81%) in exp. 10, where only 34 μmol substrate was added, indicates that the maximum ee value is nearly attained at a substrate amount of 0.5 mmol. However, competitive inhibition of the S-enzyme(s) by ethyl acetoacetate liberated by hydrolysis of the thioxo ester contributes much to the decrease of S-thiol in this series. As seen, addition of 1 ml of the oxygen analogue causes the excess of S-enantiomer to nearly vanish (exp. 16). As a consequence high optical purity of the thiol product in preparative scale experiments is possible only by controlling the substrate concentration in some way, *e.g.* by continuous feeding with pump equipment. Another way appeared to be the introduction of an organic phase, such as hexane, as shown by exp.s 7-9, in which the ee values do not decrease with increasing amounts of substrate. Apparently the distribution of the substrate between the phases secures a low concentration in the aqueous phase. Comparisons of exp.s 1 and 6, and exp.s 2 and 7 show that hexane itself does not affect the ee value neither with resting nor fermenting yeast. Initially, the use of an organic phase was tried in order to reduce hydrolysis of the substrate. This aim was attained only to a small extent.

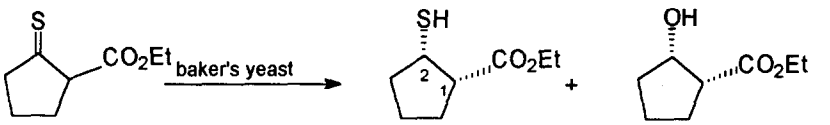
Variation of temperature (30 °C instead of 20 °C) and pH (pH ~ 8 tested) did not alter the ee value significantly (not shown in the Table). In attempts to improve the less satisfactory maximum optical purity of about 80% of the thiol **2a**, modification of substrate and yeast was tried. Changing to the butyl ester did not increase the ee value, exp. 12. On the other hand the methyl ester did not exhibit a decrease in ee, exp. 11, as is the case with the oxygen analogue. Regarding "modification" of yeast it has been reported that dry[17] and "aged" yeast[18] produce more S-products in the reduction of some β-keto esters, including ethyl acetoacetate. Therefore, it was not unexpected that dry yeast (in an amount equivalent to 25 g of fresh yeast), resting as well as fermenting, gave a fair improvement in ee, exp.s 13 and 14. The same rise in ee was obtained with ordinary yeast that had been frozen for 8 weeks, exp. 15. Thus, drying, ageing or freezing seem to weaken the activity of the R-enzyme(s).

We finally tried to control the enantioselectivity by addition of inhibitors. A large number of compounds was tested but only the interesting cases are presented in the Table. Surprisingly, allyl alcohol in low concentrations, exp. s 17 and 18, inhibits the R-enzyme(s) whereas the S-enzyme(s) is inhibited by the alcohol in higher concentration, exp. 19. Nakamura *et al.* have shown that allyl alcohol inhibits the S-enzyme(s) in baker's yeast reduction of a number of β-keto esters.[19] We have verified this in the case of ethyl acetoacetate with allyl alcohol in the concentration range used by the Japanese group. Addition of relatively large amounts of ethyl acrylate or biacetyl, exp. s 20 and 21, led to notable rises in ee values of S-thiol. Larger amounts or use of both of these inhibitors, exp. 22, gave no significant additional effect. Likewise, the effects of dry yeast and an inhibitor are not additive, exp. 23.

Reductions of the higher homologues **1d** and **1e** proceed with lower S-preferences as is the case with the oxygen analogues (see below). In experiments with an organic phase these less water soluble compounds were not fully converted (reduced or hydrolysed). Considering exp.s 24-27 it is concluded that the maximum ee at low substrate concentration is about 56% for the thioxopentanoic acid ester **1d**. Exp. 24, without the substrate concentration-moderating hexane phase, shows that in this case 0.5 mmol of substrate is a little too much to give this maximum value. Addition of an R-enzyme inhibitor raised the ee value to 80%, exp. 28. With the thioxohexanoic acid ester **1e** the maximum ee value at low substrate concentration drops to about 1.6% (still S) as deduced from exp.s 31 and 32. In this case 0.5 mmol of substrate in the water phase is far too much to give this maximum value as seen from exp. 29 where actually an excess of R-thiol is obtained. Addition of an R-en-

zyme inhibitor raised the ee value to 32%, exp. 33, whereas addition of an S-enzyme inhibitor and omitting the hexane phase gave a 73% excess of R-thiol, exp. 34. For comparison it may be noted that the oxygen analogue of **1d**, *i.e.* 3-oxopentanoic acid ethyl ester, in our laboratory, showed a maximum excess of S-alcohol of 42% with resting yeast and low substrate concentration, and a maximum excess of R-alcohol of 52% with fermenting yeast and high substrate concentration. The oxygen analogue of **1e**, *i.e.* 3-oxohexanoic acid ethyl ester, gave a large excess of R-alcohol (up to 92%) under all conditions. Thus, there is a more pronounced tendency towards R-products in the homologous series of oxo esters than in the series of thioxo esters. In a preparative scale experiment (28-fold upscaling of exp. 22), (S)-3-mercaptobutanoic acid ethyl ester was obtained in 24% yield, 93% chemical purity, and ee = 92%.

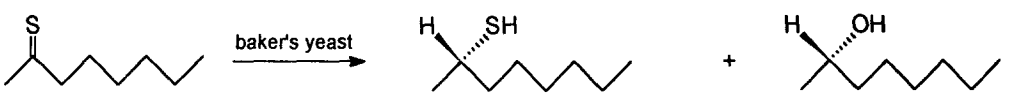
Scheme 2



4 **5** ee(1S,2S)=81% **6** ee (1R,2S)=97%

Cyclic β-keto esters also have been much investigated in microbial reductions. Remarkably high (>99%) diastereo- and enantioselectivities were found in baker's yeast reductions of 2-oxocyclopentane - and 2-oxocyclohexanecarboxylic acid ethyl ester to give almost exclusively 1R, 2S-products,[20,21] such as compound **6** in Scheme 2. In the present work the 5-ring thio-analogue **4** (Scheme 2) was selected for study. As with the acyclic thioxo esters a high ratio of fermenting yeast and substrate is crucial for reduction to compete with hydrolysis. The addition of a hexane phase is no longer useful because this substrate is too little soluble in the water phase. In a preparative scale experiment only *cis*-products **5** (27% yield after purification on silica) and **6** were obtained. The configuration of **5** was established by its formation from **6** in a sequence via tosylate and iodide. The ee values for **5** and **6** were 81 and 97%, respectively. Thus, although the reduction of thioxo ester **4** is completely diastereoselective its enantioselectivity is considerably below that of the oxygen analogue.

Scheme 3



7 **8** ee=80% **9** ee= 97%

Finally, a monofunctional thione, namely 2-octanethione, was investigated. Again, as shown in Scheme 3, the reduction of the thione was less enantioselective than that of the oxygen analogue. The configuration of thiol **8** was ascertained by its formation from (R)-2-octanol by a Mitsunobu-Volante reaction.[11] A sample of racemic 2-octanethiol was prepared by $NaBH_4$ reduction of the thione.

EXPERIMENTAL

Instruments. ^1H NMR spectra were recorded on a 250 MHz Bruker spectrometer, in $CDCl_3$ with TMS as internal standard. EI mass spectra were recorded on a VG Trio-2 instrument using the GC inlet . Optical rota-

tions were measured on a Perkin-Elmer 241 polarimeter. GC analyses were performed on a Hewlett-Packard 5890 chromatograph with a 50 m x 0.2 mm, d_f = 0.33 μm, HP-5 column with hydrogen carrier gas (~ 40 cm/s). Peak areas were measured with an HP 3394 integrator.

Carbamate derivatives for enantiomeric analysis. The thiol or alcohol (1 μl) was heated with (R)-1-phenylethyl isocyanate (3 μl) without solvent in a sealed glass capillary at 130 °C overnight. The product was dissolved in 1 ml of CH_2Cl_2 and analysed by GC at 230 °C.

(RS)-Ethyl 3-mercaptobutanoate (**2a**). Ethyl 3-(acetylthio)butanoate[22], 19.0 g (0.10 mol), (prepared in 54% yield by heating equimolar amounts of thioacetic acid and ethyl crotonate on an oilbath at 150°C overnight, analogously to the synthesis of 3-(acetylthio)butanoic acid[23]), was deacetylated with EtONa, 0.11 mol, in EtOH, 100 ml, at room temperature for 15 min. After reduction of the volume in vacuum to one third, ice and hydrochloric acid, 50 ml 2M, were added. The solution was saturated with NH_4Cl and extracted with CH_2Cl_2, 4 x 50 ml. The organic phase was dried with Na_2SO_4 and distilled to give a fraction of **2a**, 7.6 g (51%), bp_{15} 75-7°C. NMR: 1.27 (3H, t, J = 7.0), 1.37 (3H, d, J = 6.8), 1.83 (1H, d, J = 6.7), 2.55 (1H, dd, J = 7.7, 16), 2.63 (1H, dd, J = 6.5, 16), 3.37 (1H, m), 4.16 (2H, quart., J = 7.0). MS: 148 (24, M), 115 (16), 103 (13), 102 (8), 101 (10), 87 (8), 75 (31)., 74 (40), 61 (67), 60 (35), 47 (18), 42 (100).

A higher boiling fraction was identified by NMR and MS as *diethyl 3,3'-thiodibutanoate* (mixture of diastereomers), 4.0 g (30%), bp_{12} 165-70 °C. MS: 262 (17, M), 217 (8), 175 (5), 171 (13), 147 (100), 146 (35), 129 (9), 116 (10), 101 (78).

(S)-Ethyl 3-mercaptobutanoate (**2a**) *from baker's yeast reduction.* To a stirred suspension of 700 g of baker's yeast (De Danske Spritfabrikker) in 3.5 l of tap water at room temperature were added 28 ml each of ethyl acrylate and 2,3-butanedione and, after 30 min. 10.2 g (70 mmol) of ethyl 3-thioxobutanoate dissolved in 1 l of hexane. Stirring was continued for 2 days with continuous addition of 1400 g of sugar dissolved in 2 l of water. The hexane phase was separated and the aqueous suspension was extracted with 0.5 l of hexane. The combined organic phases were dried with Na_2SO_4 and distilled to give a fraction of **2a**, 2.5 g (24%), bp_{12} 76-9 °C, containing ~ 1% of alcohol **3a**, ~ 2% ethyl crotonate and ~ 3% starting material (GC), ee 92% (GC analysis of carbamate derivatives).

(S)-Ethyl 3-(acetylthio)butanoate. (S)-Ethyl 3-mercaptobutanoate, ee = 75% (from small scale yeast reduction of ethyl 3-thioxobutanoate), 88.5 mg (0.6 mmol), was stirred overnight with acetyl chloride, 0.2 ml (2.8 mmol) at room temperature. Excess acetyl chloride was removed in vacuum and the product was purified on silica (AcOEt/hexane, 1/9) to give 72 mg (63%) of the acetylated ester, $[\alpha]_D^{20} = -16.5$ (c = 1.4, $CHCl_3$). NMR: 1.27 (3H, t, J = 6.9), 1.38 (3H, d, J = 7.2), 2.30 (3H, s), 2.55 (1H, dd, J = 7.2, 15.5), 2.68 (1H, dd, J = 6.0, 15.5), 3.92 (1H, m), 4.16 (2H, quart., J = 6.9).

(R)-Ethyl 3-(acetylthio)butanoate. A solution of (S)-ethyl 3-hydroxybutanoate, ee =75% (from baker's yeast reduction of ethyl acetoacetate), 0.53 g (4 mmol), and thioacetic acid, 0.57 ml (8 mmol) in THF, 5 ml, was added during 5 min. to a stirred suspension of the addition complex of triphenylphosphine and diethyl azodicarboxylate, 8 mmol each, in 20 ml of THF at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then for 1 h at room temperature, concentrated in vacuum, diluted with 10 ml of ether and filtered. Purification on silica (AcOEt/hexane, 1/9) gave 0.40 g (53%) of the title compound, $[\alpha]_D^{20} = +15.8$ (c = 2.5, $CHCl_3$).

(S)-Ethyl 3-(acetylthio)pentanoate. (R)-Ethyl 3-hydroxypentanoate, ee = 32% (from baker's yeast reduction of ethyl 3-oxopentanoate), 1.0 g, was treated as above to give, after purification on silica (AcOEt/hexane, 1/9), 0.42 g (30%) of the title compound. NMR: 0.90 (3H, t, J = 7.0), 1.28 (3H, t, J = 7.1), 1.63 (2H, m), 2.32 (3H, s), 2.60 (1H,dd, J = 6.7, 16), 2.67 (1H, dd, J = 6.2, 16), 3.86 (1, m), 4.15 (2H, quart., J = 7.1).

(S)-Ethyl 3-mercaptopentanoate (**2d**). (S)-Ethyl 3-(acetylthio)pentanoate, 20 µl, was deacetylated in 1 ml of EtOH containing 2 drops of 10 M HCl in EtOH at 70 °C for 2 days. GC analysis of carbamate derivatives showed an ee value of about 30%. NMR: 1.03 (3H, t, J = 7), 1.27 (3H, t, J = 7), 1.65 (2H, m), 1.67 (1H, d, J = 7), 2.51 (1H, dd, J = 8.5, 15.5), 2.68 (1H, dd, J = 5.5, 15.5), 3.15 (1H, m), 4.17 (2H, quart., J = 7). MS: 162 (8, M), 133 (4), 129 (68), 117 (16), 115 (9), 101 (32), 89 (28), 88 (38), 87 (36), 83 (26), 75 (40), 56 (100), 55 (70).

(S)-Ethyl 3-(acetylthio)hexanoate. (R)-Ethyl 3-hydroxyhexanoate, ee = 88% (from baker's yeast reducton of ethyl 3-oxohexanoate), 1.0 g, was treated as above to give, after purification on silica (AcOEt/hexane, 1/9), 0.50 g (40%) of the title compound, $[\alpha]_D^{20}$ = −15.7 (c = 2.5, $CHCl_3$). NMR: 0.97 (3H, t, J = 7.2), 1.27 (3H, t, J = 7.1), 1.55-1.85 (4H, m), 2.32 (3H, s), 2.60 (1H, dd, J = 7.0, 16), 2.66 (1H, dd, J = 6.7, 16.9), 3.82 (1H, m), 4.16 (2H, quart., J = 7.1).

(S)-Ethyl 3-mercaptohexanoate (**2e**). (S)-Ethyl 3-(acetylthio)hexanoate, 20 µl, was deacetylated in 1 ml of EtOH containing 2 drops of 10 m HCl in EtOH at 70°C for 2 days. GC analysis of carbamate derivatives showed an ee value of 88%. NMR: 0.93 (3H, t, J = 7), 1.27 (3H, t, J = 7), 1.35-1.70 (4H, m), 1.69 (1H, d, J = 7), 2.52 (1H, dd, J = 8.5, 15.5), 2.68 (1H, dd, J = 5.5, 15.5), 3.22 (1H, m), 4.18 (2H, quart., J = 7). MS: 176 (9, M), 143 (77), 131 (15), 115 (21), 103 (23), 102 (19), 101 (18), 97 (69), 89 (32), 88 (35), 87 (47), 70 (79), 69 (100), 55 (78).

(1S,2S)-Ethyl 2-mercapto-1-cyclopentanecarboxylate (**5**) *from baker's yeast reduction*. To a stirred suspension of 500 g of baker's yeast in 1 l of tap water at room temperature was added 100 g of sugar and, after 15 min, 2.0 g (12 mmol) of ethyl 2-thioxo-1-cyclopentanecarboxylate. After 2 days, the suspension was extracted with 3 x 250 ml CH_2Cl_2. The extract was dried with Na_2SO_4 and concentrated in vacuum to give 1.7 g of a mixture of about 15% starting material, 45% mercaptan **5**, (*cis* isomer only), 10% ethyl 2-oxo-1-cyclopentane-carboxylate and 30% alcohol **6** (GC). Chromatography on silica (AcOEt/hexane, 2.5 /97.5) gave 0.55 g (27%) of the title compound, ee = 81% (GC analysis of carbamate derivatives), $[\alpha]_D^{20}$ = −5.9 (c = 1.0, $CHCl_3$), de =100%. NMR: 1.29 (3H, t, J = 7.0), 1.55-2.25 (6H, m), 1.68 (1H, d, J = 7.2), 3.00 (1H, m), 3.51 (1H, m), 4.18 (2H, m (d quart.), J = 7.0). MS: 174 (22, M), 141 (3), 129 (13), 128 (4), 101 (26), 99 (7), 95 (6), 86 (8), 85 (5), 73 (16), 68 (100), 67 (71), 65 (7), 55 (7), 47 (4), 45 (5), 41 (13), 39 (7), 29 (13).

(1S,2S)-Ethyl 2-mercapto-1-cyclopentanecarboxylate (**5**) *from the oxygen analogue*. To an ice-cooled solution of (1R, 2S)-ethyl 2-hydroxy-1-cyclopentanecarboxylate, ee = 95%, de = 98.6% (from baker's yeast reduction of ethyl 2-oxo-1-cyclopentanecarboxylate), 15.0 g (0.095 mol) in pyridine, 225 ml, was added tosyl chloride, 35.75 g (0.188 mol), during 20 min. The mixture was kept in the refrigerator for 16 h and poured into 1.5 l of ice and water. The aqueous mixture was extracted with 3 x 200 ml of ether. The extract was washed with 4 x 50 ml of 2 M HCl and 50 ml of water, dried with Na_2SO_4, and evaporated in vacuum without heating to give a partly crystalline raw product. Crystallization from AcOEt/hexane (by cooling with dry ice) gave *(1R, 2S)-ethyl 2-tosyloxy-1-cyclopentanecarboxylate*, (18.6 g (63%), m.p. 127-8.5 °C. NMR: 1.18 (3H, t, J = 7), 1.5-2.2 (6H, m), 2.44 (3H, s), 2.85 (1H, m), 3.9 (1H, d quart., J = 7, 10.5), 4.1 (1H, d quart., J = 7, 10.5), 5.2 (1H, m), 7.32 (2H, d, J = 8), 7.77 (2H, d, J = 8). The tosylate, 0.5 g (1.60 mmol), was refluxed in acetone, 5 ml, with KI, 1.0 g (6.0 mmol), overnight. The solvent was removed in vacuum and the residue taken up in hexane, 20 ml. The hexane solution was washed with water and $NaHCO_3$ sol., dried with Na_2SO_4, and evaporated in vacuum to give 0.34 g of a mixture of 34% ethyl 1-cyclopentenecarboxylate, 66% (*1S, 2R)-ethyl 2-iodo-1-cyclopentane carboxylate* and ~ 0.3% of the *cis* isomer (GC). Chromatography on silica (AcOEt/hexane, 1/99) gave 0.12 g (28%) of the *trans* iodide, 0.45 mmol, which was refluxed in acetone, 5 ml, with thioacetic acid, 0.046 g (0.6

mmol), and K_2CO_3, 0.090 g (0.65 mmol) for 2 days. The solvent was evaporated and replaced with CH_2Cl_2, 20 ml. The solution was washed with water and $NaHCO_3$ sol., dried with Na_2SO_4 and evaporated in vacuum. The residue was heated to 70 °C ovenight in ethanol, 10 ml, containing 5 drops of 10 M HCl in ethanol. The mixture was evaporated in vacuum and the raw product purified on silica (AcOEt/hexane, 1/99) to give 0.041 g (52%) of the title compound.

Octane-2-thione (7) was prepared in 16% yield from the ketone by reaction with H_2S[8], bp_{13} 73-5°C. The product contained about 30% of 2,2-dimercaptooctane. MS: 144 (13, M), 111 (8), 101 (2), 87 (21), 74 (100), 59 (46).

(S)-2-octanethiol (**8**) was prepared as described by Volante.[11] Starting from the (R)-alcohol with ee = 99.1% the (R)-thiol with ee = 98.9 % was obtained.

(RS)- 2-Octanethiol was prepared by $NaBH_4$ reduction of 2-octanethione.

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