Kinetic Resolution of Racemic Cyclic Sulfoxides Using Hydrolytic Enzymes

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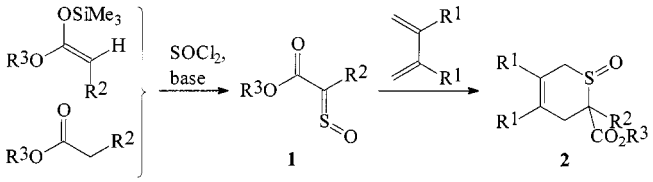
Selected racemic *trans*-2-alkoxycarbonyl-3,6-dihydro-2*H*-thiopyran *S*-oxides **2a–h** have been subjected to enzyme-assisted hydrolysis under conditions of kinetic resolution to give the corresponding acids and recovered esters with moderate to high enantiomeric purities (up to 95%). The enantioselectivity of the reaction was found to be strongly dependent on the structures of the substrates used.

Optically active sulfoxides have proved to be a very useful tool in asymmetric carbon−carbon and carbon−heteroatom bond formation and have thus found widespread application in asymmetric and stereoselective synthesis.[1] Since there is a strong demand for a great diversity of sulfoxides, the development of efficient and general methods for their synthesis remains an ongoing subject of research for organic chemists.

Among the many synthetic methodologies, those employing enzymes have recently become a valuable supplement. Thus, in addition to the well-known enzymatic oxidation of unsymmetrical sulfides,[2][3] enzyme-mediated kinetic resolution of a variety of sulfinylcarboxylates and acyloxy sulfoxides has been achieved, using commonly available hydrolytic enzymes.[4−8] Furthermore, we have demonstrated that the enzymatic methodology is also suitable for the enantioselective hydrolysis of prochiral sulfinyldicarboxylates.[9]

In our search for new types of sulfinylcarboxylates to use as substrates for enzymatic hydrolysis, we decided to investigate whether certain representatives of cyclic, six-membered sulfoxides, namely 2-alkoxycarbonyl-3,6-dihydro-2*H*-thiopyran 1-oxides **2**, could serve this purpose. It should be pointed out that these compounds have been the subject of detailed investigations by Zwanenburg et al.[10] and are easily obtainable as single diastereomers through cycloaddition reactions of butadienes with appropriate α-oxo sulfines **1** (Scheme 1).[11]

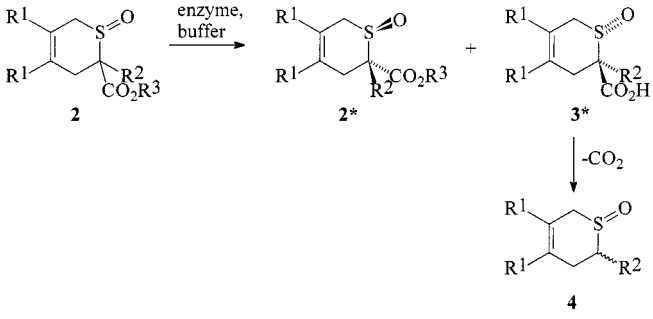
In our preliminary accounts, we reported the enzymatic resolution of three representatives of these types of substrates and the results of X-ray crystallographic studies.[12][13] In the present paper, we focus on the scope and limitations of our approach.



Scheme 1. Synthesis of thiopyran *S*-oxides **2**

Results and Discussion

Of the available cyclic sulfoxides, suitable substrates were selected for hydrolysis in the presence of some readily available enzymes. In all cases, the substrates employed were single *trans* diastereomers (vide infra). The experiments were performed in buffer solutions using an automatic titrator to maintain the appropriate pH value. The reactions were usually carried out until 50% conversion was reached, although in some cases they were deliberately stopped at different stages to obtain a better *ee* of either the unchanged ester or the hydrolysis product. The *ee* values of **2*** were determined from the ^{1}H-NMR spectra of their complexes with (+)-(*R*)-*tert*-butylphenylphosphinothioic acid, which is a versatile chiral solvating agent,[14a] especially for sulfoxides.[14b,14c] It also proved to be the reagent of choice in the case of cyclic sulfoxides. The results are summarized in Scheme 2 and collected in Table 1.



Scheme 2. Enzymatic resolution of sulfoxides **2**

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Table 1. Enzymatic hydrolysis of cyclic sulfoxides

Entry	Substrate **2**	R^1	R^2	R^3	Enzyme[a]	Yield [%] (*cis*/*trans*)[b]	Recovered ester **2*** $[\alpha]_D$ (CH_2Cl_2)	*ee* [%]	Yield [%] (*trans*/*cis*)[b]	Acid **3*** $[\alpha]_D$ (CH_2Cl_2)	*ee* [%]
1	**a**	Me	CO_2Me	Me	PLE	47	−2.0	8	Not isolated		
2	**b**	Me	CN	Et	PLE	35	+33.6	12	65[c]	−8.9[c]	n.d.
3	**b**	Me	CN	Et	α-CT	30	−132.5	48	[c]	[c]	n.d.
4	**b**	Me	CN	Et	PPL	10	−180.0	65	[c]	[c]	n.d.
5	**c**	Me	Ph	Me	PLE	No reaction					
6	**c**	Me	Ph	Me	PPL	No reaction					
7	**d**	H	Ph	Me	PLE	No reaction					
8	**d**	H	Ph	Me	α-CT	No reaction					
9	**e**	Me	Me	Me	α-CT	67	−16.1	60	30	−25	>90
10	**e**	Me	Me	Me	PLE	48	−9.6	36	50	+9.6 (+10.1[d])	38
11	**f**	H	Me	Me	PLE	30	+8.0	>95[e]	50	−6.4[f]	40
12	**f**	H	Me	Me	α-CT	No reaction					
13	**g**	Me	H	Me	α-CT	47.3, (2.25)[b]	−92.5	*cis:* 82 *trans:* 87	33 (15.7)[b,d]	+107 (+115[d])	*trans:* 93 *cis:* [g]
14	**g**	Me	H	Me	PLE	52 (1.59)[b]	+74.3	*cis:* 50 *trans:* 45	30 (>15)[b,d]	−10.5	n.d.
15	**h**	H	H	Me	α-CT	52 (2.58)[b]	−43.4	*cis:* 25 *trans:* 24	20 (11.2)[b,d]	+25 (+32[d])	*trans:* 77 *cis:* [g]
16	**h**	H	H	Me	PLE	35 (2.18)[b]	+140.0	*cis:* >95[e] *trans:* >95[e]	50	−20.3	n.d.

n.d. − not determined. − [a] PLE: porcine liver esterase; α-CT: α-chymotrypsin; PPL: porcine pancreas lipase. − [b] Only for **2g** and **2h**: separate *ee* values for each diastereomer are given wherever possible. − [c] An epimeric mixture of **4** was obtained. − [d] After reesterification with $MeOH/H_2SO_4$. − [e] None of the other enantiomer was detected. − [f] In methanol. − [g] Difficult to measure due to signal overlap.

The first two sulfoxides used, viz. **2a** and **2b**, possess an additional electron-withdrawing substituent at C-2. They turned out to be fairly good substrates for enzyme-assisted hydrolysis and gave the recovered esters **2*** with low to moderate enantioselectivities. The main drawback, however, was the loss of the acidic products of the hydrolysis due to spontaneous decarboxylation under the reaction conditions used. Hence, in the case of **2a**, no defined product could be isolated, while in the case of **2b** a mixture of diastereomeric 2-cyano sulfoxides **4** was formed. In turn, the two 2-phenyl derivatives **2c** and **2d**, which were supposed to allow the isolation of both reaction products, proved to be completely unreactive, irrespective of the enzymes or conditions applied. The observed difference in reactivity between these two types of substrates might be attributed to their structural characteristics. X-ray diffraction analyses of **2b** and **2d** revealed that although both compounds have the *trans* configuration, they adopt wholly different conformations.[13] Thus, in **2b** the ester group and the sulfinyl oxygen occupy equatorial positions, while in **2d** both these groups are axial; consequently, the cyano group in **2b** is axial and the phenyl group in **2d** is equatorial. Using PLE, this finding can account for the observed reactivity differences by reference to Tamm′s PLE substrate model. According to this model,[15] the optimal acceptance of the substrate by PLE is achieved when a polar function and the reacting ester group are in a *trans* arrangement and, in the case of cyclic substrates, particularly six-membered ones, when the ester group occupies an equatorial position. Assuming that the conformations observed in the solid state predominate in buffer solutions, the ability of **2b** to undergo PLE-mediated hydrolysis could be explained by the equatorial orientation of its ester function, while the lack of reactivity of **2d** may be attributed to the axial orientation of this group. However, no such explanation can be invoked for the other enzymes used. The steric hindrance exerted by the phenyl group is most probably responsible for the lack of reactivity of **2c** and **2d**.

To check this assumption, new substrates **2e** and **2f**, bearing a small, non-polar methyl group at C-2 were prepared. It is noteworthy that this synthesis involved the first application of the isolated α-oxo sulfine **1** (R^2 = Me, R^3 = Me) as a substrate in a Diels−Alder reaction with butadienes. A number of α-oxo sulfines, which were previously considered to be too unstable to be obtained in a pure state, survived the isolation and purification procedures, including distillation![10d] The use of pure **1** substantially increased the yields of the cycloadducts **2e** and **2f** in comparison with the in-situ procedure employed previously.

Enzymatic hydrolyses of **2e** and **2f** were found to proceed smoothly to give both the recovered esters **2*** and the corresponding acids **3*** with good or, in some cases, almost complete stereoselectivities. A comparative X-ray crystallographic analysis of **2e** (Figure 1) revealed that it has the *trans* configuration and adopts a conformation identical to that of **2d**,[13] i.e. with the methoxycarbonyl group and the sulfinyl oxygen occupying axial positions. This result clearly shows that in this case the axial orientation of the ester group does not prevent its enzymatic hydrolysis. Hence, the presence of a bulky phenyl group at C-2 seems to be solely responsible for the lack of reactivity of **2c** and **2d**.

Apart from the above considerations, some surprising observations emerged that merit further comment. Firstly, the two substrates, **2e** and **2f**, which are very closely related (differing only by the presence of two methyl groups at the remote C-4 and C-5), were found to show totally different preferences for particular enzymes. Thus, **2e** undergoes hydrolysis in the presence of α-chymotrypsin (α-CT) with a much higher stereoselectivity than in the presence of PLE, whereas with **2f** no reaction is observed in the presence of

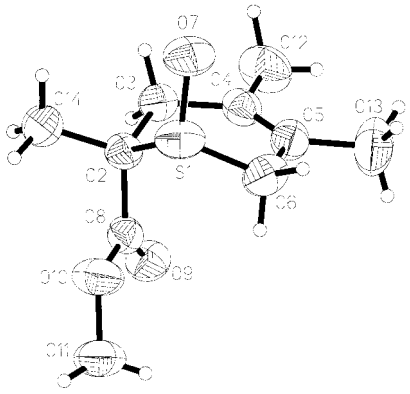

Figure 1. Molecular structure of **2e** with crystallographic numbering

α-CT, while its PLE-mediated hydrolysis leads to **2*f** with an *ee* value in excess of 95%. Secondly, the optical rotation values of **2*e** and particularly of **2*f** are unusually low compared to those of other types of sulfoxides.[1] At present, we can offer no adequate explanation for these facts. Evidently, small structural changes in the substrates have a dramatic impact on the ability of the enzyme to accommodate them in its active site.

The encouragingly high enantioselectivities observed in the aforementioned experiments prompted us to extend our investigations to the cycloadducts **2g** and **2h**, in spite of the fact that the presence of the acidic hydrogen may lead to epimerization at C-2. Gratifyingly, the cycloadducts were obtained as single diastereomers. Their X-ray crystallographic analyses (Figures 2 and 3) unambiguously showed the *trans* configuration and, as in the case of **2b**,[13] a sofa conformation with the sulfinyl oxygen and the ester group occupying equatorial positions.

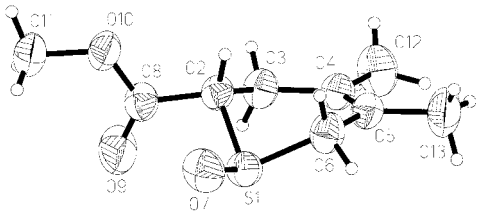

Figure 2. Molecular structure of **2g** with crystallographic numbering

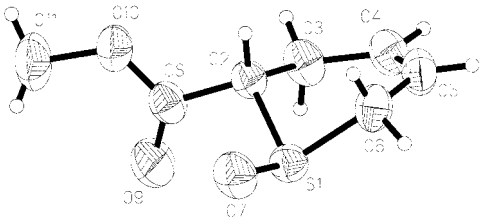

Figure 3. Molecular structure of **2h** with crystallographic numbering

Their enzyme-mediated hydrolysis proceeded smoothly and both the unchanged esters and the acids could be isolated in good yields. However, in all cases investigated, the recovered ester turned out to be a mixture of C-2 epimers. A control experiment, in which the substrates were maintained under the conditions employed for the enzymatic hydrolysis, revealed that both **2g** and **2h** were epimerized to give a mixture of *cis* and *trans* diastereomers. The acids **3*** obtained from the hydrolysis were re-esterified with excess methanol in the presence of a catalytic amount of concentrated sulfuric acid. Interestingly, the methyl esters obtained in this way were found to consist largely of the *trans* diastereomers (up to 95%). In another control experiment, the diastereomeric mixture of the recovered ester **2*g** (*cis*/*trans* ratio 2.25, Table 1, entry 13) was subjected to the same conditions and thereafter the new *cis*/*trans* ratio was found to be 0.7, proving that the equilibrium is shifted towards the *trans* epimers at lower pH.

Although the epimerization caused some complications, the enzymatic approach proved to be quite efficient. Thus, ^{1}H-NMR spectra of **2*g** and **2*h**, recorded in the presence of (+)-(*R*)-*tert*-butylphenylphosphinothioic acid, indicated that the products remained enantiomerically enriched, in some cases with *ee*′s exceeding 95%. Inspection of the data in Table 1 reveals that the presence or absence of methyl groups at C-4 and C-5 of the substrate is of importance with regard to the enantioselectivity of particular enzymes. Thus, α-chymotrypsin was more stereoselective towards **2g** (entry 13 vs. 15) while PLE was more stereoselective towards **2h** (entry 16 vs. 14), which resembles the situation with **2e** and **2f** (vide supra). It is noteworthy that the *ee* values of each pair of epimers were nearly the same (±5%). On the basis of this observation, it can be assumed that only one of the two diastereomers of the substrate undergoes hydrolysis, the other one being epimerized prior to the reaction. Since, according to Tamm′s model, the *trans* epimers should be preferentially accommodated in the active site of PLE, their very high content in the esters obtained by esterification of the corresponding acids **3*** may also favour this assumption.

In conclusion, cyclic 2-alkoxycarbonyl sulfoxides **2** are fairly good substrates for enantioselective, enzyme-assisted hydrolysis, with the exception of derivatives bearing a bulky substituent at C-2, which do not react. Moreover, the enantioselectivity of the hydrolysis shows a much higher dependence on the structural characteristics of the substrates than in the case of their open-chain analogues. Epimerization at C-2, as observed for **2g** and **2h**, which have a hydrogen atom at this carbon, does not influence the stereogenic centre at the sulfur; as a consequence, the two interconverting epimers retain the same enantiomeric excess.

Experimental Section

General: Phosphate buffer solutions were purchased from Aldrich. Ammonium sulfate suspension of porcine liver esterase (PLE) was purchased from either Fluka or Sigma. Other enzymes were purchased form Fluka. A 0.2 M solution of NaOH was used in an automatic titrator to adjust the pH of the hydrolysis mixtures.

^{1}H-NMR spectra were recorded at 100, 300, 400, and 500 MHz with Bruker instruments, in $CDCl_3$ solution. − Optical rotations

were measured on a Perkin−Elmer 241 MC photopolarimeter. − Melting points were measured on a Boetius apparatus and are uncorrected. − Column chromatography was carried out using Merck 60 silica gel; TLC was performed on Merck 60 F_{254} silica gel plates.

Synthesis of Substrates

(*E*)-Methoxycarbonyl Methyl Sulfine (1) ($R^2 = R^3 = Me$): A solution of 1-methoxy-1-trimethylsilyloxy-1-propene (11.4 g, 71.5 mmol) and diisopropylethylamine (12.5 mL) in dry diethyl ether (100 mL) was added dropwise at −78°C to a solution of $SOCl_2$ (5.2 mL, 71.5 mmol) in 80 mL of diethyl ether. The resulting mixture was stirred at −78°C for 1 h and then allowed to warm to room temperature. The precipitate formed was filtered off and the ether was evaporated to give crude **1** as a yellowish, offensive smelling liquid (8.8 g, 93%). Careful distillation under reduced pressure provided an analytically pure product as a colorless liquid (6.3 g, 66%); b.p. 49°C at 16 mmHg. − ^{1}H NMR (100 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, C-CH_3), 3.87 (s, 3 H, OCH_3). − ^{13}C NMR (25 MHz, $CDCl_3$): δ = 13.3 (*C*H_3-C), 52.5 (CH_3-O), 163.8 (C=O), 182.4 (C=S). − GC-MS (EI); *m*/*z* (%): 135 (100) [M^+], 102 (69), 59 (36) [CH_3OOC^+].

Synthesis of Thiopyran *S*-Oxides 2: The synthesis of **2a**, **b**, **c**, **d** has been described previously.[10,11,13]

***trans*-2-Methoxycarbonyl-2,4,5-trimethyl-3,6-dihydro-2*H*-thiopyran *S*-Oxide (2e):** To a solution of sulfine **1** ($R^2 = R^3 = Me$) (3.5 g, 26.1 mmol) in CH_2Cl_2 (100 mL), 2,3-dimethylbutadiene (6 mL, 52 mmol) was added in one portion and the mixture was stirred overnight at room temperature. After evaporation of the solvent and subsequent column chromatography of the residue (hexane/AcOEt, gradient 4:1→0:1), a yellowish oil was obtained, which solidified on standing. Recrystallization from *i*Pr_2O gave an analytically pure product (4.82 g, 85%); m.p. 59−60°C. − ^{1}H NMR ($CDCl_3$): δ = 1.56 (s, 3 H, CH_3-C), 1.74 (br. s, 6 H, CH_3-C=C), 2.48 (br. s, 2 H, C-CH_2-C), 3.03 and 3.50 (AB, 2 H, *J* = 17 Hz, S-CH_2C), 3.70 (s, 3 H, CH_3O). − MS (EI); *m*/*z*: 216 [M^+].

***trans*-2-Methoxycarbonyl-2-methyl-3,6-dihydro-2*H*-thiopyran *S*-Oxide (2f):** Starting from sulfine **1** (5.75 g, 42.9 mmol) and 1,3-butadiene (excess, condensed at −78°C), **2f** was obtained as a colorless oil (5.65 g, 70%) after column chromatography (hexane/AcOEt, gradient 2:1→0:1). Alternatively, starting from **1** (0.67 g, 5.0 mmol), 1,3-butadiene (excess), and $SnCl_4$ (10 mol%), thiopyran *S*-oxide **2f** was obtained after similar work-up as a low-melting solid; m.p. ca. 30°C. − ^{1}H NMR (100 MHz, $CDCl_3$): δ = 1.62 (s, 3 H, C-CH_3), 2.4−2.7 (m, 2 H, C-CH_2-C), 3.29 (A of AB, br. d, *J* = 18.0 Hz, 1 H, C-CH_AH_BS), 3.50 (B of AB, br. d, *J* = 18.0 Hz, 1 H, C-CH_AH_BS), 3.77 (s, 3 H, OCH_3), 5.52−5.97 (m, 2 H, CH=CH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6 (C-*C*H_3), 27.4 (C-*C*H_2-C), 44.9 (C-*C*H_2-S), 52.8 (OCH_3), 59.9 (*C*-CH_3), 116.4 and 126.8 (*C*H-*C*H), 171.8 (C=O). − MS (CI); *m*/*z* (%): 189 (100) [M^+ + 1], 189.5, 140 (63). − $C_8H_{11}O_3S$ (188.2): calcd. C 51.05, H 6.43, S 17.03; found C 50.40, H 6.54, S 17.05.

***trans*-2-Methoxycarbonyl-4,5-dimethyl-3,6-dihydro-2*H*-thiopyran *S*-Oxide (2g):** 2,3-Dimethylbutadiene (7 mL, 6-fold excess) and $SOCl_2$ (1.19 g, 10 mmol) were dissolved in diethyl ether (40 mL) and the mixture was cooled to −78°C while argon was passed through it. To this, a solution of triethylamine (1.1 g, 11 mmol) and *tert*-butyldimethylsilyloxy-1-methoxyethene (1.88 g, 10 mmol) in diethyl ether (40 mL) was added dropwise. The resulting mixture was left at room temperature overnight and then washed with water and brine. The aqueous layers were extracted with diethyl ether and then with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and the solvents were evaporated. The crude residue was purified by column chromatography (hexane/AcOEt, gradient 4:1→0:1) to give pure **2g** (1.36 g, 68%) as a yellowish solid; after crystallization from *i*Pr_2O or toluene/hexane, m.p. 53−55°C. − ^{1}H NMR ($CDCl_3$): δ = 1.74 (br. s, 6 H, CH_3-C=C), 2.48−2.78 (m, 2 H, C-CH_2C), 3.30 (A of AB, br. d, *J* = 15.4 Hz, 1 H, C-CH_AH_B-S), 3.55 (B of AB, br. d, *J* = 15.4 Hz, 1 H, C-CH_AH_B-S), 3.80 (s, 3 H, OCH_3), 3.86 (dd, *J* = 7.6 Hz, 5.6 Hz, 1 H, CH). − ^{13}C NMR ($CDCl_3$): δ = 19.2 and 19.8 (*C*H_3-C=C-*C*H_3), 30.1 (C-*C*H_2-S), 52.5 (*C*-CH_2-S), 52.7 (OCH_3), 61.8 (CH), 117.2 and 126.7 (-*C*=*C*-), 168.8 (C=O). − MS (FAB); *m*/*z* (%): 203 (100) [M^+ + 1].

***trans*-2-Methoxycarbonyl-3,6-dihydro-2*H*-thiopyran *S*-Oxide (2h):** Gaseous 1,3-butadiene was condensed into the reaction flask at −78°C and dissolved in diethyl ether (120 mL). $SOCl_2$ (2.2 mL, 30 mmol) was added and then a solution of 1-butyldimethylsilyloxy-1-methoxyethene (5.64 g, 30 mmol) and triethylamine (4.2 mL, 30 mmol) was added dropwise. The dry-ice condenser was kept in position throughout to avoid evaporation of the butadiene. After stirring for 10 h at −78°C, the mixture was left at room temperature overnight, allowing evaporation of the excess butadiene. Work-up and purification were carried out as described for **2g**. Compound **2h** (2.7 g, 52%) was obtained as a slightly yellow solid; crystallization from *i*Pr_2O afforded the pure product, m.p. 85−88°C. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.72 (A of AB, d of m, *J* = 17.3 Hz, 1 H, C-CH_AH_BC), 2.83 (B of AB, d of m, *J* = 17.3 Hz, 1 H, C-CH_AH_B-C), 3.36 (A of AB, d of m, *J* = 16.9 Hz, 1 H, C-CH_AH_B-S), 3.66 (B of AB, d of m, *J* = 16.9 Hz, 1 H, C-CH_AH_B-S), 3.82 (s, 3 H, OCH_3), 3.92 (dd, *J* = 7.6 Hz, 5.3 Hz, 1 H, CH), 5.61−5.64 and 5.89−5.92 (m, 2 H, HC=CH). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.1 (C-*C*H_2-C), 47.2 (C-*C*H_2-S), 53.0 (OCH_3), 60.6 (CH), 117.2 and 127.1 (C-*C*=*C*-C), 168.8 (C=O). − MS (EI); *m*/*z* (%): 174 (2) [M^+], 142 (23), 126 (100), 111 (41), 97 (28), 67 (87), 59 (40) [CH_3COOC^+]. − $C_7H_{10}O_3S$ (174.220): calcd. C 48.26, H 5.79, S 18.40; found C 48.64, H 5.36, S 17.73.

General Procedure for the Enzymatic Hydrolysis of 2: To a stirred solution of ester **2** (1 mmol) in 20 mL of phosphate buffer (pH 7.2−7.5) at 30°C, was added the enzyme (PLE: 20−40 μL, α-CT: 5−10 mg). The pH was kept constant by the continuous addition of 0.2 M aqueous NaOH using an automatic titrator. When the desired degree of conversion was reached (e.g. after 2.5 mL of NaOH had been added dropwise), the reaction was quenched by adding 200 mL of acetone and the mixture was cooled in a freezer for ca. 3 h. It was then filtered though Celite and the acetone was evaporated. The residue was extracted with CH_2Cl_2 (5 × 10 mL) and the combined extracts were dried with $MgSO_4$. The solvent was evaporated and the crude product was purified by silica gel chromatography (as described above for the racemic substrates) to give pure unchanged esters **2*** (see Table 1). The remaining aqueous layer was acidified with H_2SO_4 (to ca. pH 3.0) and the water was evaporated under reduced pressure or the sample was lyophilized. The residue was extracted several times with CH_2Cl_2, the combined extracts were dried, and the solvent was evaporated to give acids **3***.

In certain cases, the acid was dissolved in excess methanol, a drop of concentrated H_2SO_4 was added, and the solution was left for 2−3 days. In this time, the acid **3*** was re-esterified to the methyl ester **2*** of opposite absolute configuration. The methanol was then evaporated, the residue was taken-up in CH_2Cl_2, and this solution was washed with a small amount of water and dried with $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (as above) to give the esters (see Table 1).

Determination of the Diastereomeric Ratio and Enantiomeric Excess for 2g and 2h: Although neither *cis*-**2g** nor *cis*-**2h** were isolated in

a pure state, their presence and structures were deduced from the ^{1}H-NMR spectra of the diastereomeric mixtures. The data given below were obtained by subtracting the spectra of the *trans* diastereomers from the spectra of the relevant mixtures. The most important feature of the *cis* diastereomers is that the O-CH_3 signals are shifted by ca. 0.02−0.03 ppm downfield from those of the *trans* diastereomers; these signals allowed the *ee* values of each epimer to be determined, as they were split when the spectra were measured in the presence of an equimolar amount of (+)-(*R*)-*tert*-butylphenylphosphinothioic acid (chiral solvating agent).

cis-**2g:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (br. s, 6 H, CH_3-C=C), 2.38−2.44 (br. AB, 2 H, C-CH_2C), 2.92−3.00 (m, 2 H, C-CH_2-S), 3.39 and 3.42 (dd, *J* = 12.0 Hz, 4.72 Hz, 1 H, CH), 3.83 (s, 3 H, OCH_3).

cis-**2h:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54−2.63 and 2.91−2.99 (dm, 2 H, C-CH_2-C), 3.37−3.50 (m, 2 H, C-CH_2-S), 3.62−3.64 and 3.66−3.68 (dm, 1 H, CH), 3.84 (s, 3 H, OCH_3), 5.62−5.66 and 6.00−6.04 (dm, 2 H, H-C=C).

Crystallographic Data

***trans*-2-Methoxycarbonyl-2,4,5-trimethyl-3,6-dihydro-2*H*-thiopyran (2e):** The crystal and molecular structure was determined using data collected at room temperature on a CAD4 diffractometer with graphite-monochromated Cu-K_α radiation. Compound **2e** crystallizes in the monoclinic system with space group $P2_1/c$, with the unit cell consisting of 8 molecules. Crystal data and experimental details are given in Table 2. The lattice constants were refined by a least-squares fit of 25 reflections in the θ range 24.28−31.64°. The decrease in the intensities of three control reflections (0,9,−8; −1,10,−2; 2,3,−7) amounted to 8.4% during an exposure time of 110.7 h and hence an intensity correction was applied (DECAY program).[16] An empirical absorption correction was applied using the ψ-scan method (EAC program).[16][17] A total of 4591 reflections with $I \geq 2\sigma(I)$ were used to solve the structure by direct methods and to refine it by full-matrix least-squares[18][19] on F^2. Hydrogen atoms were located on a difference Fourier map and were re-

Table 2. Crystal data and experimental details of compounds **2e**, **2g** and **2h**

Compound	**2e**	**2g**	**2h**
Molecular formula	$C_{10}H_{16}O_3S$	$C_9H_{14}O_3S$	$C_7H_{10}O_3S$
Formula weight	216.29	202.26	174.21
Crystallographic system	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a [Å]	7.1240(10)	10.837(3)	7.2090(10)
b [Å]	19.874(4)	8.761(3)	8.532(2)
c [Å]	15.823(3)	11.506(4)	13.308(3)
α [°]	90.00	−	−
β [°]	92.96(3)	106.12(3)	94.93(3)
γ [°]	90.00	−	−
V [Å^3]	2237.3(7)	1049.5(6)	815.5(3)
Z	8	4	4
D_{calcd} [g/cm^3]	1.284	1.280	1.419
μ [cm^{-1}]	14.28	25.54	31.97
Crystal dimensions [mm]	0.24 × 0.42 × 0.60	0.20 × 0.25 × 0.25	0.15 × 0.30 × 0.80
Maximum 2θ [°]	150	150	150
Radiation, λ [Å]	Cu-K_α, 1.54184	Cu-K_α, 1.54184	Cu-K_α, 1.54184
Scan mode	ω/2θ	ω/2θ	ω/2θ
Scan width [°]	0.75 + 0.14 tanθ	0.86 + 0.14 tanθ	0.86 + 0.14 tanθ
hkl ranges:	$0 \leq h \leq 8$	$-13 \leq h \leq 13$	$0 \leq h \leq 9$
	$-24 \leq k \leq 24$	$-10 \leq k \leq 10$	$-9 \leq k \leq 0$
	$-19 \leq l \leq 19$	$0 \leq l \leq 14$	$-16 \leq l \leq 16$
DECAY correction: min.	1.00002	1.00003	−
max.	1.04500	1.02425	−
ave.	1.02214	1.01138	−
EAC correction: min.	0.9110	0.8966	0.8886
max.	0.9995	0.9987	0.9993
ave.	0.9673	0.9553	0.9538
No. of reflections: unique	4591	2157	1565
with $I > 0\sigma(I)$	4591	2070	1515
obsd. with $I > 2\sigma(I)$	4187	−	−
No. of parameters refined	382	175	141
Largest diff. peak [eÅ^{-3}]	0.415	0.310	0.238
Largest diff. hole [eÅ^{-3}]	−0.331	−0.230	−0.301
shift/e.s.d. max	0.001	0.000	0.001
R_{obs}	0.0412	0.0387	0.0396
wR_{obs}	0.1084	0.1082	0.1134
S_{obs}	1.043	1.057	1.043
weighting coeff.[a] m	0.0636	0.0578P	0.0756
n	0.4092	0.2217	0.2646
extinction coeff.[b] k	0.0092(5)	0.0161(13)	0.0218(18)
R_{int}	0.0367	0.0361	0.0171
$T_{meas.}$	293(2)	293(2)	293(2)
F(000)	928	432	368

[a] Weighting scheme $w = [\sigma^2(Fo^2) + (mP)^2 + nP]^{-1}$, where $P = (Fo^2+2Fc^2)/3$. − [b] Extinction method *SHELXL*, extinction expression $Fc^* = kFc[1 + 0.001 \times Fc^2\lambda^3/\sin(2\theta)]^{-1/4}$.

fined isotropically. Anisotropic thermal parameters were refined for all non-hydrogen atoms. The final refinement converged to R = 0.0412 for 4187 observed reflections with $I \geq 2\sigma(I)$ and 382 refined parameters.

The elemental lattice contains two almost identical molecules, of which one is depicted in Figure 1.

***trans*-2-Methoxycarbonyl-4,5-dimethyl-3,6-dihydro-2*H*-thiopyran *S*-Oxide (2g):** The crystal and molecular structure was determined using data collected at room temperature on a CAD4 diffractometer with graphite-monochromated Cu-K_α radiation. Compound **2g** crystallizes in the monoclinic system with space group $P2_1/c$, with the unit cell consisting of 4 molecules. Crystal data and experimental details are given in Table 2. The lattice constants were refined by a least-squares fit of 25 reflections in the θ range 18.46−29.26°. The decrease in the intensities of three control reflections (−1,2,6; −1,−4,4; −1,−2,5) amounted to 4.7% during an exposure time of 45.1 h and hence an intensity correction was applied (DECAY program).[16] An empirical absorption correction was applied using the ψ-scan method (EAC program).[16][17] A total of 2157 unique reflections were used to solve the structure by direct methods and to refine it by full-matrix least-squares on F^2 (F set to zero for negative F^2).[18][19] Hydrogen atoms were located on a difference Fourier map and were refined isotropically. Anisotropic thermal parameters were refined for all non-hydrogen atoms. The final refinement converged to R = 0.0387 for 175 refined parameters and 2070 observed reflections with $I \geq 2\sigma(I)$.

***trans*-2-Methoxycarbonyl-3,6-dihydro-2*H*-thiopyran *S*-Oxide (2h):** The crystal and molecular structure was determined using data collected at room temperature on a CAD4 diffractometer with graphite-monochromated Cu-K_α radiation. Compound **2h** crystallizes in the monoclinic system with space group $P2_1/c$, with the unit cell consisting of 4 molecules. Crystal data and experimental details are given in Table 2. The lattice constants were refined by a least-squares fit of 25 reflections in the θ range 18.62−30.50°. The decrease in the intensities of three control reflections (−1,3,−4; 2,2,4; 2,3,−3) amounted to just 1.3% during an exposure time of 34.8 h. An empirical absorption correction was applied using the ψ-scan method (EAC program).[16][17] A total of 1565 unique reflections were used to solve the structure by direct methods and to refine it by full-matrix least-squares on F^2 (F set to zero for negative F^2).[18][19] Hydrogen atoms were located on a difference Fourier map and were refined isotropically. Anisotropic thermal parameters were refined for all non-hydrogen atoms. The final refinement converged to R = 0.0396 for 141 refined parameters and 1515 observed reflections with $I \geq 2\sigma(I)$.

Crystallographic data for **2e**, **2g**, and **2h** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-117645, CCDC-112862, and CCDC-112863, respectively.[20]

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[1] M. Mikołajczyk, J. Drabowicz, P. Kiełbasiński, *Chiral Sulfur Reagents: Applications in Asymmetric and Stereoselective Synthesis*, CRC Press, Boca Raton, **1997**.
[2] For reviews see: [2a] H. Holland, *Chem. Rev.* **1988**, *88*, 473−485. − [2b] S. Colonna, N. Gaggero, *Phosphorus, Sulfur and Silicon* **1994**, *95−96*, 103−111.
[3] S. Colonna, N. Gaggero, G. Carrea, P. Pasta, *J. Chem. Soc., Chem. Commun.* **1997**, 439−440 and references therein.
[4] H. Ohta, Y. Kato, G. Tsuchihashi, *Chem. Lett.* **1986**, 217−218.
[5] [5a] K. Burgess, I. Henderson, *Tetrahedron Lett.* **1989**, *30*, 3633−3636. − [5b] K. Burgess, I. Henderson, K.-K. Ho, *J. Org. Chem.* **1992**, *57*, 1290−1295.
[6] S. G. Allenmark, A. C. Andersson, *Tetrahedron: Asymmetry* **1993**, *4*, 2371−2376.
[7] C. Cardellicchio, F. Naso, A. Scilimati, *Tetrahedron Lett.* **1994**, *35*, 4635−4638.
[8] A. N. Serreqi, R. J. Kazlauskas, *Can. J. Chem.* **1995**, *73*, 1357−1367.
[9] M. Mikołajczyk, P. Kiełbasiński, R. Żurawiński, M. W. Wieczorek, J. Błaszczyk, *Synlett* **1994**, 127−129.
[10] [10a] J. B. M. Rewinkel, Ph. D. Thesis, University of Nijmegen, **1989**. − [10b] R. C. De Laet, A. J. J. M. van Breemen, A. J. Derksen, M. van Klaveren, B. Zwanenburg, *Phosphorus, Sulfur and Silicon* **1992**, *74*, 371−372. − [10c] R. C. De Laet, Ph. D. Thesis, University of Nijmegen, **1995**. − [10d] T. J. G. Damen, Ph. D. Thesis, University of Nijmegen, to be completed in **1999**.
[11] B. G. Lenz, H. L. M. Regeling, B. van Rozendaal, B. Zwanenburg, *J. Org. Chem.* **1985**, *50*, 2930−2934.
[12] P. Kiełbasiński, M. Mikołajczyk, B. Zwanenburg, R. C. De Laet, *Phosphorus, Sulfur and Silicon* **1994**, *95−96*, 495−496.
[13] M. W. Wieczorek, J. Błaszczyk, B. Dziuba, P. Kiełbasiński, M. Mikołajczyk, B. Zwanenburg, J. B. M. Rewinkel, *Heteroatom Chem.* **1995**, *6*, 631−638.
[14] [14a] For a recent application, see: J. Drabowicz, B. Dudziński, M. Mikołajczyk, S. Colonna, N. Gaggero, *Tetrahedron: Asymmetry* **1997**, *8*, 2267−2270 and references therein. − [14b] J. Drabowicz, B. Dudziński, M. Mikołajczyk, *Tetrahedron: Asymmetry* **1992**, *3*, 1231. − [14c] M. Mikołajczyk, W. Perlikowska, J. Omelańczuk, H.-J. Cristau, A. Perraud-Darcy, *J. Org. Chem.* **1998**, *63*, 9716−9722.
[15] P. Mohr, N. Waespe-Sarcevic, C. Tamm, K. Gawronska, J. K. Gawroński, *Helv. Chim. Acta* **1983**, *66*, 2501−2511.
[16] B. A. Frenz, *SDP-Structure Determination Package*, Enraf-Nonius, Delft, The Netherlands, **1984**.
[17] A. C. T. North, D. C. Philips, F. S. Mathews, *Acta Cryst.* **1968**, *A24*, 351.
[18] G. M. Sheldrick, G. M. Kruger, R. Goddard, *SHELXS-86*, Crystallographic Computing 5, Oxford, **1982**.
[19] G. M. Sheldrick, *SHELXL-97*, University of Göttingen, **1997**.
[20] Copies of the data can be obtained free of charge on application to the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, U.K [Fax (internat.) +44 (0)1223/ 336033; e-mail: deposit@ccdc.cam.ac.uk].

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