Pergamon

Tetrahedron Vol. 50, No. 16, pp. 4775-4794, 1994
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0040-4020/94 $6.00+0.00

0040-4020(94)E0136-H

Catalytic Kinetic Resolution Of 5-Alkoxy-2(5H)-Furanones

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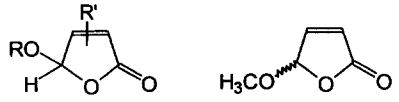
Abstract: The kinetic resolution of racemic 5-alkoxy-2(5H)-furanones, using a chiral aminoalcohol catalyzed 1,4-addition of arylthiols, was examined. Using various butenolides it was shown that a γ-alkoxy substituent appears to be essential to reach high enantioselectivities whereas electron-donating substituents in the arylthiols also increase the selectivity. Cinchona alkaloids are the preferred catalysts for the kinetic resolution, with quinine and quinidine leading to the most efficient and selective thiol additions. A remarkable dilution effect and a strong dependency on the mode of addition of reactants were observed. Optimization studies are presented of the kinetic resolution of 5-methoxy-2(5H)-furanone **2** resulting in (R)-**2** or (S)-**2** with enantiomeric excesses exceeding 90%. A mechanism for the quinine (quinidine) catalyzed kinetic resolution is given.

Optically active γ-substituted butenolides are encountered frequently in a number of natural products, especially in flavor components and insect sex pheromones[1]. Furthermore these butenolides are considered to be useful as chiral synthons for the preparation of terpenoidal lactone pheromones, antileukeamic lignans, (-)-verrucarinolactone, prostacycline analogues, chrysanthemic acid, polyoxin J, (-)-ranunculin, lasalocid A and various other biologically active natural products[1d].

Optically active alkyl-substituted butenolides have been obtained from natural resources such as carbohydrates, ascorbic acid, tartaric acid and l-glutamic acid and from synthetic compounds such as chiral α-acetylenic acids, chiral hydroxy-sulfoxides, chiral epoxides and other chiral materials[1c,1d].

Not unexpected a large number of synthetic applications of alkylbutenolides have been reported[2,3]. On the contrary γ-alkoxybutenolides **1** were only recently explored and showed to be attractive synthons due to their multifunctional nature and diversity of chemical transformations, i.e. cycloadditions, 1,4-additions and acetal chemistry, that can be envisaged[4,5].



1 **2**

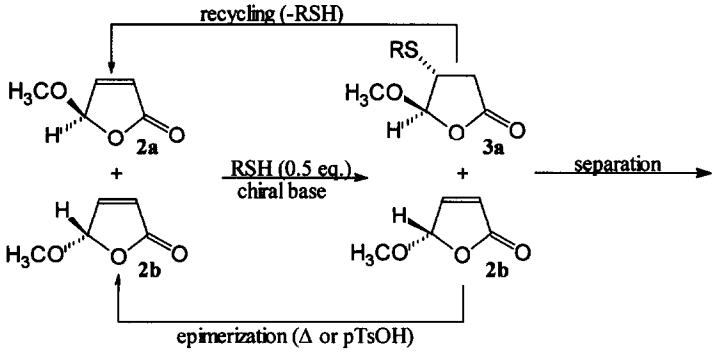
Figure 1

Exploring the reactivity of racemic 5-methoxy-2(5H)-furanone **2** Farina and co-workers[6] and Feringa and De Lange[7] found several new routes to acyclic and heterocyclic products. γ-Alkoxybutenolides have also been used in the total synthesis of pilocarpine[8a], camptopthecine[8b], verrucarin J[8c], manoalide[8d,e] and dl-strigol[8f], the latter being a highly potent seed germination stimulant for the root parasite witchweed (Striga lutea Lour). In these total syntheses γ-alkoxybutenolides were only used as racemates.

New strategies in asymmetric synthesis based on optically active γ-menthyloxybutenolides have been developed by us[4,5,9]. Except for γ-menthyloxy-2(5H)-furanone[4], which is an auxiliary based chiral synthon that combines uniform high diastereoselectivity with chemical flexibility, the enantiomerically pure γ-alkoxybutenolides are in general not easily accessible. A route to optically active γ-alkoxybutenolides **1** which is not auxiliary based, and preferentially a catalytic route, would be highly desirable. In this paper we describe the attempts to achieve kinetic resolution[10] of racemic 5-methoxy-2(5H)-furanone **2** to enantiomerically pure 5(R)-**2** or 5(S)-**2** by means of cinchona alkaloid catalyzed thiophenol 1,4-addition reactions. Cinchona alkaloids have previously been applied as catalysts in the kinetic resolution of α,ß-unsaturated ketones[11]. For example Hiemstra and Wynberg showed that 5-methyl-cyclohexen-2-one could be obtained with an optical purity of 33% via the 1,4-addition reaction of p-t-butylthiophenol catalyzed by cinchonidine[11a].

Kinetic resolution of 5-alkoxyfuranones by 1,4-addition of thiols

The catalytic kinetic resolution we envisaged is shown in Scheme 1. 1,4-Addition reactions of thiophenols to 5-methoxy-2(5H)-furanone **2** take place at room temperature in the presence of a catalytic amount of triethylamine to give a quantitative yield of thiophenol adducts[7c]. Complete trans diastereoselective Michael type addition occurred in all cases. In the presence of catalytic amounts of a chiral base, preferential addition of the thiol to (R)-5-methoxybutenolide **2a** could provide mainly **3a**, whereas the S-enantiomer **2b** remains unconverted, depending upon the "selectivity factor"[10] for this particular addition.



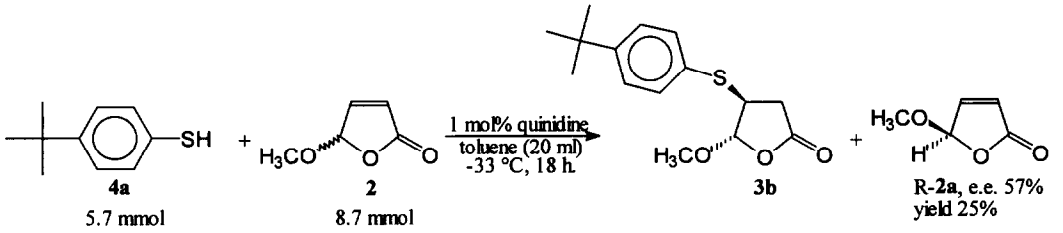
Scheme 1

To be synthetically useful the adduct **3** and the remaining starting material should be readily separable without loss of stereochemical integrity. Furthermore enantioselectivities should exceed 90%. Major advantages of the scheme shown are the possibility to recycle the unwanted isomer either by

thiol elimination from adduct **3a** or via epimerization of the enriched butenolide **2b** to the racemic mixture. It has previously been shown that adducts such as **3a** are prone to thiol elimination at higher temperatures or under strong basic conditions[7c] and that butenolide epimerization can be readily accomplished[4,5].

In preliminary experiments the addition of 0.5 equivalents of thiophenol to racemic **2** was performed at room temperature in the presence of a catalytic amount (0.8 mol%) of l-cinchonidine as a chiral base, according to Scheme 1. The remaining starting material (yield 40%) in this kinetic resolution process showed an optical purity of 13%. Various optimizations were performed next. In particular by using different chiral bases and p-t-butylthiophenol **4a** and by performing the reactions at lower temperatures (vide infra).

To determine the dependency of the enantiomeric excess on several reaction variables, the following kinetic resolution process was chosen as our standard reaction (Scheme 2).

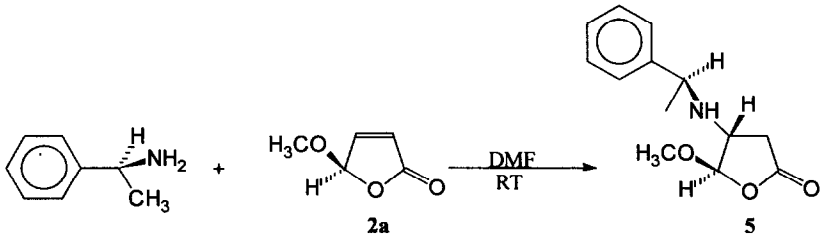


Scheme 2

Thus the addition of 0.65 equivalents of p-t-butylthiophenol **4a** to racemic **2** in 20 ml of dry toluene at -33°C, with quinidine as the chiral catalyst, provides (R)-**2a** in 25% yield (based on a maximum yield of 35%) with an enantiomeric excess (e.e) of 57%.

Determination of the enantiomeric and optical purity and absolute configuration of 2a

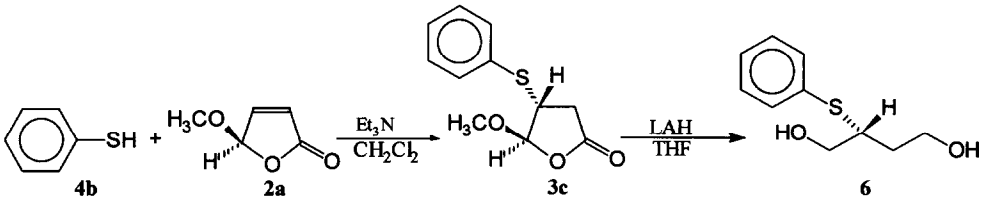
The enantiomeric excess of the recovered 5-methoxy-2(5H)-furanone **2** was determined via the addition of (l)-α-methylbenzylamine to **2** in DMF at room temperature (Scheme 3). Amine addition to 5-methoxy-2(5H)-furanone shows complete diastereofacial control and gives the amine-adduct **5** in quantitative yield[7a,12].



Scheme 3

For the diastereomeric addition products **5**, obtained from racemic **2** and (l)-α-methyl-benzylamine, clearly separated absorptions for the acetal-hydrogens in the ^{1}H NMR spectrum are observed. From the integration of these signals, the diastereomeric excess (d.e.) of **5** (and therefore the e.e. of **2**) can be calculated and in the case of the standard reaction the e.e. was found to be 57%.

For the standard reaction the optical purity and absolute configuration of recovered **2a** were also independently determined by means of conversion into 2-phenylthio-1,4-butanediol[7c,13] (Scheme 4). The addition of thiophenol **4b** to **2** also proceeds quantitative and diastereoselective[7c], whereas (R)-**6** and (S)-**6** were also prepared in enantiomerically pure form from (5R)- or (5S)-γ-menthyloxy-2(5H)-furanone [7c].



4b **2a** **3c** **6**

Scheme 4

For optically pure (R)-**6** $[\alpha]_D^{20}$= +40.2° (c 3.5, MeOH) and for optically pure (S)-**6**: $[\alpha]_D^{20}$= -41.7° (c 3.5, MeOH) have been reported[7c,13].

After kinetic resolution under the standard conditions, the recovered (-)-5-methoxy-2(5H)-furanone **2** showed a specific rotation of $[\alpha]_D^{20}$= -80.5° (c 1, $CHCl_3$). The 2-phenylthio-1.4-butanediol **6**, synthesized according to Scheme 4, showed for this particular case a specific rotation of $[\alpha]_D^{20}$= +22.5° (c 3.2, MeOH). From the positive sign of the rotation it can be concluded that the R-enantiomer of **6** was synthesized. Because no racemization was expected in the synthesis of **6**[7c,13] it can be deduced that recovered (-)**2a**, after kinetic resolution under the standard conditions, has the R-configuration. An optical purity (o.p.) of 56% was calculated for (R)-**2a**. This value is in good agreement with the e.e. calculated from the ^{1}H NMR data (e.e.= 57%).

The influence of the structure of the butenolide

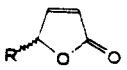
Kinetic resolutions have also been performed with 5-isopropoxy-2(5H)-furanone **7** and 5-n-butyl-2(5H)-furanone **8**. The idea was that a more bulky group at the 5-position of the butenolide might lead to higher enantioselectivities. The results are summarized in Table 1.

Under the standard conditions at -33 °C, **7** shows a too slow reaction. Total conversion of p-t-butyl-thiophenol **4a** was achieved after 24 hours at room temperature. The e.e. as well as the o.p. of recovered **7** were determined in an analogous way as was done for **2a** (vide supra). With the resolution of **8**, total conversion of thiol was obtained after 40 hours at -33 °C. Because the maximum specific rotation of **8** is known from the literature[15], the optical purity could readily be calculated after measurement of the specific rotation of recovered **8**. From entries 1-3 it is clear that increasing the size of the γ-alkoxy substituent or the use of a γ-alkylbutenolide does not lead to higher selectivities.

To assess the influence of the stereogenic center at the γ-position an asymmetric synthesis was performed by the addition of thiophenol **4b** to 2(5H)-furanone **9** under the standard conditions. The

optical purity of the addition product, 4-phenylthio-butyrolactone, was determined after reduction to 2-phenylthio-1,4-butanediol **6**, according to Scheme 4. This asymmetric 1,4-addition may be compared with the cinchona alkaloid mediated addition of 2-cyclopenten-1-one and p-t-butylthiophenol[11a]. In that case the addition product was obtained with 5% e.e. and the R absolute configuration. The selectivity in the case of **9** is poor although somewhat higher than for 2-cyclopenten-1-one. If p-t-butylthiophenol is used as a nucleophile, the selectivity may further increase (vide infra Table 3, entry 6). From these experiments it is evident that the presence of the γ-alkoxy substituent is important in order to reach high selectivities and that a balance between conversion time and enantioselectivity has to be found.

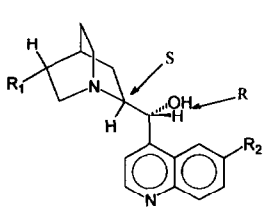
Table 1: Influence of the structure of the butenolide.

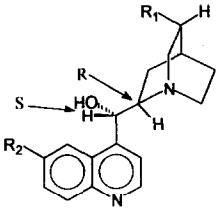
entry	 R		reaction temp./time (°C, h.)	yield[a] (%)	$[\alpha]_D^{20}$ degrees	e.e. (%)	absolute configuration[c]
1	MeO	**2**	-33, 18	25	-80	57	R
2	iPrO	**7**	21, 24	26	-16	19 (16)[b]	R
3	nBu	**8**	-33, 40	16	+11.5	11[b]	S
4	H	**9**	-33, 24	63	-5.6	14[b]	S

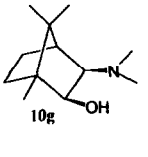
a. yield of recovered butenolide, max. yield 35%; b. optical purity; c. absolute configuration of enantiomer remaining in excess; entry 4. asymmetric synthesis using thiophenol **4b**

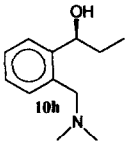
The influence of the structure of the catalyst

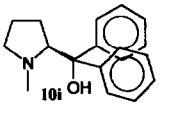
Cinchona alkaloids, shown in Figure 2, have been applied in the standard reaction. Furthermore some chiral tertiary aminoalcohols (Fig. 2), which have been successfully applied in the synthesis of chiral arylalcohols[16], were used as catalysts. The results are summarized in Table 2.











	R_1	R_2
10a quinine	C_2H_3	OCH_3
10b cinchonidine	C_2H_3	H
10c dihydroquinine	C_2H_5	OCH_3

	R_1	R_2
10d quinidine	C_2H_3	OCH_3
10e cinchonine	C_2H_3	H
10f dihydroquinidine	C_2H_5	OCH_3

10g, DAIB= (-)-3-exo-dimethylaminoisoborneol
10h, HDAMB= (1-hydroxypropyl)-2-(dimethylaminomethyl)-benzene
10i, DPMPM= (S)-(+)-diphenyl-(1-methylpyrrolidin-2-yl)-methanol

Figure 2: Structures of cinchona alkaloids and other tertiary aminoalcohols used in the kinetic resolution of 5-methoxy-2(5H)-furanone **2**.

Table 2: Influence of the structure of the catalyst upon the enantioselectivity of the kinetic resolution of butenolide **2**

entry[a]	catalyst		conversion[b] (%)	yield[c] (%)	$[\alpha]_D^{20}$ degrees	e.e. (%)	absolute configuration[d]
1	quinidine	**10d**	99	25	-80	57	R
2	quinine	**10a**	99	24	+62	56	S
3	cinchonidine	**10b**	94	23	+47	40	S
4	cinchonine	**10e**	85	27	-35	24	R
5	dihydroquinine	**10c**	99	25	+52	47	S
6	dihydroquinidine	**10f**	99	18	-50	43	R
7	DAIB	**10g**	97	20	+6	8	S
8	HDAMB	**10h**	91	32	+0.5	0.2	S
9	DPMPM	**10i**	89	15	+18	19	S

a. 1-6: 18 h. at -33 °C; 7, 8, 9: after respectively 8, 9 and 28 days at RT

b. conversion of p-t-butylthiophenol **4a**

c. isolated yield of recovered **2**

d. absolute configuration of the enantiomer remaining in excess

From Table 2 it can be seen that both enantiomers of 5-methoxy-2(5H)-furanone are accessible. The chiral center directly adjacent to the tertiary nitrogen in the catalyst determines which enantiomer of the starting material is selectively converted. For example quinine (**10a**, entry 2), with the S-configuration at C_8 and the R-configuration at C_9 (Fig. 2), causes enrichment of the S enantiomer of **2** (56% e.e.), while quinidine (**10**, entry 1) having the R-configuration at C_8 and the S-configuration at C_9, provides the R-enantiomer of **2** (57% e.e.). From the studies on cinchona alkaloid catalyzed enantioselective additions, it is known that quinine and quinidine as well as cinchonine and cinchonidine behave as pseudoenantiomers[11,16,17].

In spite of small structural changes between the cinchona alkaloids, significant differences in the e.e's are found. The best results are obtained with quinidine **10d** and quinine **10a** as chiral catalysts. Cinchonidine **10b** and cinchonine **10e** give lower e.e.'s, partially also because of lower arylthiol conversion. This in turn may be explained in terms of the lower solubility of **10b** and **10e**, compared to the other cinchona alkaloids. It is not directly clear in which way the methoxy-substituent (R_2, Fig. 2) in quinidine and quinine influences the e.e. of the reaction.

The tertiary aminoalcohols **10g**, **10h**, **10i**, preferentially convert the R-enantiomer of **2**, however with poor e.e.'s. Moreover these catalysts give very long reaction times at room temperature, probably because they are less strong bases. It should be noted that in accordance with earlier observations the aminoalcohol moiety seems to be essential for effective catalysis[11a].

Influence of the structure of the arylthiol

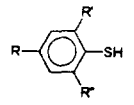
The standard reaction was executed with seven different arylthiols. The structures of the nucleophiles and the results of the kinetic resolution of **2** are shown in Table 3.

The acidity constants (pK_A) of meta and para substituted arylthiols depend on the nature of the substituents[18]. In 1,4-additions of thiols a thiol-base complex is assumed as an intermediate in a steady state concentration, which then reacts with the α,ß-unsaturated ketone[19]. The extent to which the arylthiol proton is transferred to the base-catalyst e.g. -the nature of the ion pair- will be dependent on the pK_A of the arylthiol and this may well influence the enantioselectivity of the reaction[20].

All arylthiols gave complete reactions after 18 h. at -33°C, except for **4f**, which only gave sufficient reaction at room temperature (entry 5). Probably 2,4,6-trimethylthiophenol **4f**, with two ortho methyl substituents, is sterically too hindered to give addition under the standard reaction conditions. Electron-donating substituents in the arylthiol seem to have a positive influence on the e.e.. With substituents in the ortho position steric effects may become important as is shown for **4f** (entry 5).

The best results sofar were obtained with 2,4-diisopropylthiophenol **4g** (entry 7) as nucleophile. Compared to the standard reaction with **4a** a small improvement in the e.e. of recovered **2** was measured.

Table 3: Influence of the structure of the arylthiol[a].

entry	 R R' R"				yield[b] (%)	$[\alpha]_D^{20}$ degrees	e.e. (%)	absolute configuration[d]
1	Cl	H	H	**4c**	33	-17	6	R
2	H	H	H	**4b**	23	-41	29	R
3	MeO	H	H	**4d**	23	-57	46	R
4	Me	Me	H	**4e**	22	-60	48	R
5	Me	Me	Me	**4f**	21	+2	<1	S[c]
6	tBu	H	H	**4a**	25	-80	57	R
7	iPr	iPr	H	**4g**	22	-80	62	R

a. quinidine as catalyst, reaction temperature -33 °C

b. isolated yield of recovered **2**

c. reaction completed at RT

d. absolute configuration of the enantiomer remaining in excess

The influence of the temperature

The ratio of the specific rate constants k_R and k_S for the 1,4-addition will be temperature dependent. If the reaction shows a positive activition enthalpy, as is usually the case, the selectivity will increase for reactions performed at lower temperature, as can be deduced from the Arrhenius equation. The results of the standard conversion of **2** at several temperatures are shown in Table 4. All reactions were run till

complete conversion of p-t-butylthiophenol.

As can be seen from Table 4, the kinetic resolution reaction shows a great enhancement in the selectivity at lower reaction temperatures. Compared to the standard reaction conditions (vide supra) a significant improvement in the e.e. was obtained at a temperature of -51 °C (entry 4) indicating a positive reaction enthalpy of the thiol addition reaction.

Table 4: Influence of the reaction temperature.

entry	temp. (°C)	yield[a] (%)	$[\alpha]_D^{20}$ degrees	e.e. (%)
1	+40	19	-37	26
2	+21	23	-36	24
3	-33	25	-80	57
4	-51	24	-84	69

a. isolated yield of recovered **2**

The influence of the amount of the catalyst

As we observed that the kinetic resolution was sensitive to catalyst concentration, we examined this effect in more detail. The standard reaction was executed with less quinidine (**10d**). With 0.2 mol% of the catalyst no reaction was found after 18 h. at -33 °C (Table 5, entry 1). Using 0.5 mol% quinidine **10d**, total conversion of the arylthiol **3a** was found after 5 days at -33 °C. The amount of the catalyst used in the 1,4-thiol addition reaction has a drastic effect on the e.e. of recovered **2a**. Using 0.5 mol% quinidine **10d** (entry 2), the measured e.e. was 71%, which is a significant improvement compared to the e.e. of 57% of the standard reaction. Unfortunately the reaction time also increases drastically when less catalyst is used. The higher enantioselectivity is probably caused by the decrease in polarity of the reaction medium when less catalyst is added[11, 19].

Table 5: Influence of the amount of catalyst[a].

entry	catalyst (mol %)	time (h)	yield[b] (%)	$[\alpha]_D^{20}$ degrees	e.e. (%)
1	0.2	18	-	-	-
2	0.5	120	28	-89	71
3	1	18	25	-80	57

a. quinidine **10d** was used as catalyst

b. isolated yield of recovered **2a**

Influence of the concentration of the reactants

From reactions performed at room temperature first an effect of the amount of solvent on the e.e. was seen (Table 6). It appeared that dilution caused a significant increase in selectivity (entries 1-3). Therefore a second effect was examined, namely the mode of addition. Either butenolide **2** or thiol **4a** were slowly added to the reaction mixture at -33 °C, during a 2.5 hours period of time.

In the case of slow addition of p-t-butylthiophenol **4a**, this resulted in poor conversions (conversion only 55%, after 18 h. at -33 °C), probably because the solubility of the catalyst decreases. It seems that the alkaloid catalyst is solubilized in the presence of thiol. When on the contrary **2** was slowly added to the reaction mixture, containing all the other ingredients, an improvement of the e.e. was found (entry 5). The procedure in which **2** was slowly added, was repeated at -51 °C with 0.65 eq. **4a** (entry 6) and with 0.75 eq. **4a** (entry 7). In this way it was possible to raise the enantiomeric excess in recovered γ-alkoxybutenolide **2a** over 90%.

Table 6: Influence of the concentration of the reactants.

entry	toluene (ml)	temp. (°C)	yield[a] (%)	$[\alpha]_D^{20}$ degrees	e.e. (%)
1	6.5	RT	25	-29	10
2	13	RT	21	-37	21
3	20	RT	23	-36	24
4	26.5	RT	25	-40	21
5	20[b]	-33	24	-79	66
6	20[b]	-51[c]	27	-114	85
7	20[b]	-51[d]	21	-120	91

a. isolated yield of recovered **2**

b. **2** slowly added during a 2.5 h. period of time

c. 18 h. at -51 °C (93% conv.) and 24 h. at -28 °C (98% conv.)

d. 18 h. at -51 °C (83% conv.) and 24 h. at -28 °C (98% conv.)

entry 7: 0.75 eq. of **2** was used; entries 6,7: work-up by means of flash chromatography

Kinetic measurements

The course of the kinetic resolution of **2** can be followed very convenient via polarimetric experiments. First the optical rotation (α) of the reaction mixture was recorded as a function of time, for the standard reaction at 21 °C, using equimolar amounts of p-t-butylthiophenol **4a** and 5-methoxy-2(5H)-furanone **2** and 0.5 mol% quinidine **10d**. The optical rotation was found to pass through a maximum value (α_{max}) at time t= t_{max} (Figure 3). The optical rotation furtheron decreases to the value caused by the rotation of the catalyst, indicating complete reaction.

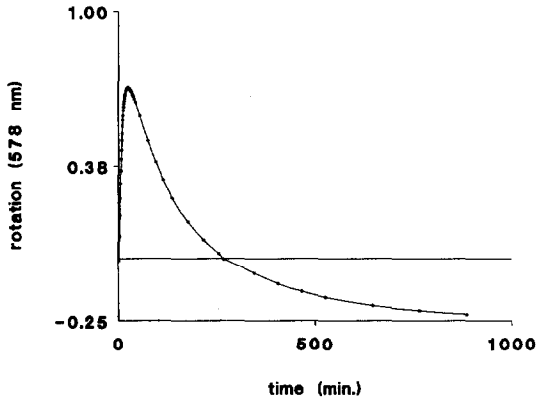


Figure 3: Optical rotation (α) of the reaction mixture as a function of time for the standard reaction. (equimolar amounts of reactants were used with quinidine as the chiral catalyst).

Second a series of polarimetric experiments were performed with the standard reaction at various temperatures between 18.5- 40 °C, using 0.65 equivalents of thiol **4a**. In this case typical plots as depicted in Figure 4 were obtained.

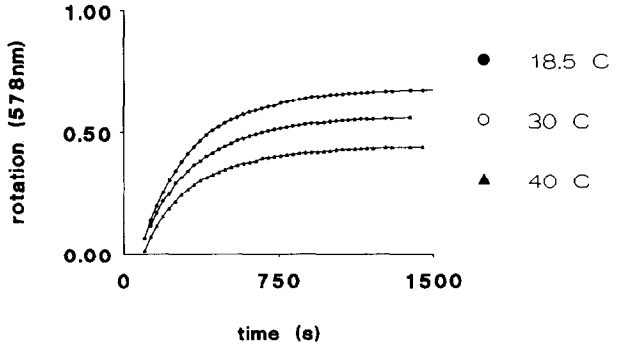


Figure 4: Evolution of the optical rotation (α) of the reaction mixture in time at various temperatures for the standard reaction, using 0.65 eq. **4a**.

From these polarimetric data the second order rate constants were deduced. The optical rotation data were treated in a similar way as was done for the second order quinidine catalyzed thiol addition to cyclohexenone[11a]. Since the catalyst concentration is essentially constant, the standard reaction shows

pseudo second order kinetics. It was assumed that the product concentration is directly proportional to the corrected rotation of the reaction mixture (the observed rotation minus the constant rotation value of the catalyst[11a]). However the optical rotation of the reaction mixture in the kinetic resolution is not only determined by the rotation of the addition product but also by the rotation caused by the enriched 5-methoxy-2(5H)-furanone **2a**. The latter rotation will also be directly proportional to the rotation of the reaction mixture and will furthermore be dependent on the rotation of the addition product[11a].

The proportionality constant for the conversion of the rotation data into concentration values was obtained by dividing the theoretical final concentration of the product by the corrected value of the final rotation (α_{max}). By applying the general equation for second order kinetics with unequal starting concentrations of the reagents **2a** and **4a**, the following equation could be derived.

$$t = \frac{1}{k_{obs.}.[cat].([\mathbf{2}]_0 - [\mathbf{4a}]_0)} \ln \frac{(\alpha_{max} - \alpha_t.[\mathbf{4a}]_0/[\mathbf{2}]_0)}{(\alpha_{max} - \alpha_t)}$$

By plotting $\ln \frac{(\alpha_{max} - \alpha_t.[\mathbf{4a}]_0/[\mathbf{2}]_0)}{(\alpha_{max} - \alpha_t)}$ (= ln X) against time t, a straight line was obtained (Figure 5).

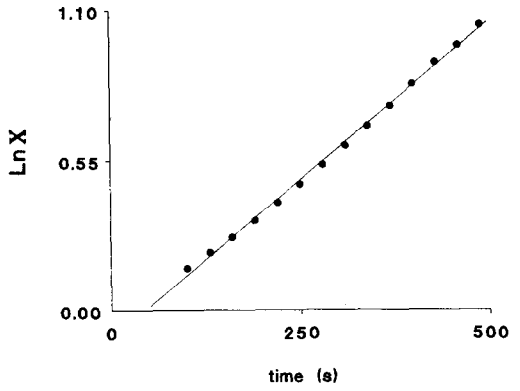


Figure 5: Pseudo second order plot for the standard reaction of Scheme **2**, reaction temperature 18.5 °C.

The lines were drawn from 14 polarimetric data points and the calculated least squares correlation coefficients were at least 0.999. Reaction constants were determined at five different temperatures between 18.5- 40 °C, as shown in Table 7.

Table 7: Second order rate constants calculated from polarimetric experiments.

t (°C)	$[2]_0$ (mol/kg)	$[\mathbf{4a}]_0$ (mol/kg)	$k_{graph.}$ ($*10^{-3}$)	$k_{obs.}$ ($kg^2/mol^2.s$)
18.5	0.454	0.299	2.32	3.73
25	0.469	0.302	2.2	3.33
30	0.477	0.298	2.41	3.35
35	0.451	0.293	2.40	3.76
40	0.466	0.295	2.43	3.52

[cat]= 4.03 mmol/kg

It is evident that the standard thiol addition reaction of Scheme 2 obeys (pseudo) second order reaction kinetics. It has to be noted that the calculated rate constants (k_{obs}) really are mean values of the rate constants of both enantiomers (k_R and k_S).

Although it was assumed that the rotation α_t does not depend on the medium and a linear correlation[21] exists between the rotation and enantiomeric excess of **2** and **4a**, sufficiently accurate correlations were found for second order behavior.

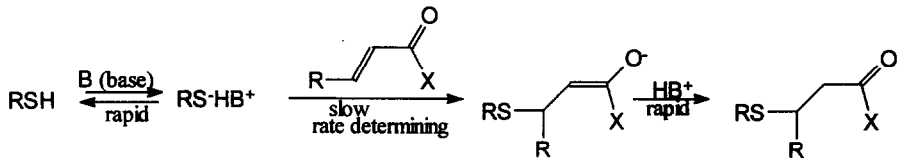
Unfortunately within the temperature range of 18.5 to 40 °C, the rate constants do not show regular variation with temperature. For this reason, activation parameters could not be determined from these data. These findings are in agreement with the results in Table 4, entries 1 and 2, as at 21°C and 40°C comparable enantioselectivities were found. At present we have no satisfactory explanation for these findings.

Mechanism of the kinetic resolution.

As already indicated above, there is a strong resemblance between the kinetic resolution described here and the catalytic enantioselective thiol addition as described by Wynberg and co-workers[11a,22]. There is a substantial amount of evidence for the formation of ternairy complexes in the key sulfide bond forming step[22].

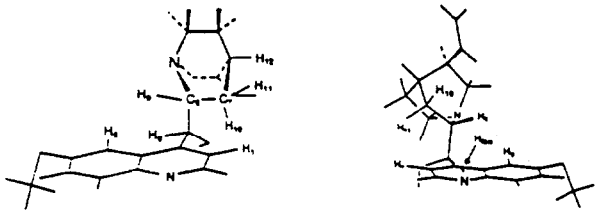
The first step in the cinchona alkaloid catalyzed thiol-addition reaction is the formation of an ion-pair between the thiol and the quinuclidine nitrogen[22a]. Because the quinuclidine nitrogen is about 3-4 pK_A units more basic than the quinoline nitrogen[19], protonation of the quinuclidine nitrogen is preferred.

The thiol-base ion-pair reacts with the α,β-unsaturated carbonyl compound in the rate determining step (Scheme 5). An enolate anion will arise, which takes up the proton of the protonated chiral base to give the product. The formation of an enolate anion is very unfavourable in apolar non hydrogen-bonding solvent. In the case of cinchona alkaloid catalysis, this process can be facilitated by the presence of a hydrogen bond between the hydroxyl group of the cinchona alkaloid and the enolate oxygen, originating from the enone[11a]. In this way the negative charge is better delocalized and the free energy of the transition state is lowered.



Scheme 5

In a conformational study of the cinchona-alkaloid catalyzed Michael addition, Dijkstra, Kellogg and Wynberg have recently described a conformational analysis of quinine and quinidine by a combined NMR and molecular modelling approach[22a,b]. Three different minimum energy conformations were obtained for quinine, while four low energy conformations were found for quinidine. The most stable conformation for quinine and quinidine in solution appeared to be the "open" conformation, in which the quinoline ring is turned away from the quinuclidine ring (Figure 6). In case of the "open" conformation the nitrogen lone-pair is freely accessible to ligand or solute. The alkaloid conformations do not change upon formation of an ion pair[22b].



quinidine quinine

Figure 6: Preferred conformations of quinidine **10d** and quinine **10a**

From results obtained by a combined molecular docking and NMR study, two diastereomeric transition states for the quinine catalyzed thiophenol addition to cyclohexenone were proposed[21a]. One of these diastereomeric transition states is unfavourable because of steric repulsion between the ring moiety of cyclohexenone opposite to the double bond and the quinoline ring of the alkaloid (quinine). It is not far fatched to suggest that the same basic mechanism (Scheme 5) is operating for 1,4 addition of thiols to γ-alkoxybutenolides and enones.

The observed selectivity in the kinetic resolution of 5-methoxy-2(5H)-furanone **2** can be explained, with the aid of the results found by Dijkstra[22]. Kinetic resolution of **2**, using quinine **10a** as a catalyst (Table 2, entry 2) causes enrichment of the S-enantiomer of 5-methoxy-2(5H)-furanone **2**. The most favourable transition state in this case, is therefore the one that leads to conversion of (R)-5-methoxy-2(5H)-furanone **2a**. Assuming a similar transition state -involving a ternairy complex- as proposed for the quinine catalyzed thiophenol addition to cyclohexenone, the transition state that leads to conversion of the R enantiomer of **2** can be depicted as shown in Figure 7.

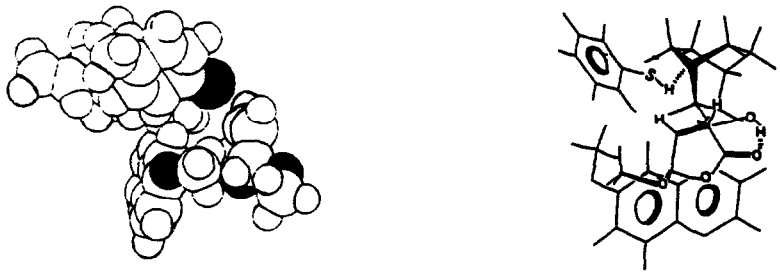


Figure 7: Transition state of the quinine catalyzed thiophenol addition to (R)-5-methoxy-2(5H)-furanone **2a**.

In the transition state, the carbonyl group of (R)-5-methoxy-2(5H)-furanone **2a** becomes hydrogen bonded to the hydroxyl-functionality of quinine **10a**, whereas the thiophenol forms an ion-pair with the quinuclidine nitrogen. Steric repulsion between the ring moiety of 5-methoxy-2(5H)-furanone opposite to the double bond and the quinoline ring is unlikely to occur. Therefore (R)-5-methoxy-2(5H)-furanone **2a** is situated with its double bond directed to the thiol sulfur and the furanone ring oxygen directed towards the quinoline ring of quinine **10a**. For steric reasons the 5-methoxy group is directed away from the quinoline ring system.

(S)-5-Methoxy-2(5H)-furanone **2b** will not react in this arrangement, because of steric repulsion of its 5-methoxy group with the quinoline ring. In the case of the S-enantiomer the oxygen of the furanone ring will be directed towards the thiol sulfur atom, whereas the ring double bond is pointed towards the quinoline ring of quinine **10a**. Therefore the transition state that leads to conversion of (S)-5-methoxy-2(5H)-furanone **2b** is less favourable because the oxygen of the furanone ring now meets with repulsive interactions of the partially negative sulfur atom of the thiophenol reagent.

All other used butenolides (**7**, **8**, **9**, Table 1) react with the same preference as 5-methoxy-2(5H)-furanone **2**, the most favourable transition state being the one with the furanone ring oriented with the double bond towards the sulfur and the oxygen in the furanone ring directed away from the sulfur of the thiophenol.

The formation of the ternairy complex of catalyst, thiol and butenolide as shown here provides also a good working model for further optimization studies as well as design of new catalysts with enhanced enantioselectivities.

It can be concluded that catalytic kinetic resolution of γ-methoxy-2(5H)-furanone has been accomplished with e.e.'s exceeding 90%. To reach these high selectivities careful control of addition mode, temperature and concentrations of reactants are required.

Acknowledgements: The cooperation with Dr. B. de Lange is gratefully acknowledged. We thank Dr. G.D.H. Dijkstra, Prof. R.M. Kellogg and Prof. H. Wynberg for helpful discussions.

Experimental section

General remarks:

^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer R-24B spectrometer (60 MHz). For e.e determinations ^{1}H NMR spectra were recorded on a Varian VXR 300 spectrometer (300 MHz). As a solvent for the ^{1}H NMR measurements $CDCl_3$ was used. Chemical shifts are denoted in δ units (ppm), relative to tetramethylsilane (TMS) as an internal standard at δ= 0 ppm. ^{13}C NMR spectra were recorded on a Varian VXR-300 (at 76.9 MHz) using $CDCl_3$ as solvent. The chemical shifts are denoted in δ units (ppm) with the solvent as an internal standard and converted to the TMS scale using δ ($CDCl_3$) = 76.91 ppm. The splitting patterns are designated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), dq (double quartet), se (septet), m (multiplet) and br (broad). Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in a 10 cm cell.
Solvents were distilled and dried if necessary. Tetrahydrofuran was distilled from sodium/benzophenone under nitrogen atmosphere. Toluene was distilled from sodium/benzophenone and stored on molecular sieves (4A). Methylene chloride was distilled from phosphorus pentoxide and stored on molecular sieves (4A). Methanol was distilled from magnesium and stored on 3A-sieves. Dimethylformamide was stored on 4A-sieves. Other solvents and reagents were used as obtained from Aldrich or Janssen Chimica, unless otherwise stated, except silica gel 60 mesh which was obtained from Merck.

GC-analyses

All conversions were determined by GC-analysis on a Hewlett-Packard 5890 gas-chromatograph, equipped with a HP-1 (15m x 0.53mm x 2.65μm) capillary column. For GC-experiments a time temperature program was used: 5 min. 120 °C; from 120 to 290 °C with a temperature increase of 60 °C/min; total run time 10 min.. Injection and detection temperature were set at 300 °C. Typical retention times were as follows: 5-methoxy-2(5H)-furanone **2**, t_R= 2.4 min.; p-t-butylthiophenol **4a**, t_R= 4.4 min. and 5-methoxy-4-(p-t.butylphenylthio)-butyrolactone **3b**, t_R= 7.7 min..

Butenolides

The following butenolides were prepared according to the literature: 5-methoxy-2(5H)-furanone[7c,26] **2**, 2(5H)-furanone[23] **9**, 5-n-butyl-2(5H)-furanone[14a,b] **8**. 5-Isopropoxy-2(5H)-furanone[26] **7** was prepared in a similar way as 5-methoxy-2(5H)-furanone **2**. A solution of 60 g (0.6 mol) 5-hydroxy-2(5H)-furanone was heated at reflux in 500 ml isopropanol. After 3 days refluxing, the conversion to **7** was complete according to the ^{1}H NMR. The solvent was removed by rotatory evaporation and the residue distilled to give 58 g (0.41 mol) 5-isopropoxy-2(5H)-furanone as a pale yellow oil, yield 68% (b.p. 67-68°C, 1 mmHg). ^{1}H NMR: 1.2 (d, 6H, H7), 4.0 (se, 1H, H6), 5.9 (s, 1H, H5), 6.1 (d, 1H, J=6Hz, H3), 7.1 (d, 1H, J=6Hz, H4)

Arylthiols

The arylthiols: p-t-butylthiophenol[24a] **4a**, p-methoxythiophenol[25d] **4d**, 2,4-dimethylthiophenol[25a] **4e**, 2,4,6-trimethylthiophenol[25c] **4f** and 2,4-diisopropylthiophenol[25b] **4g** were prepared by reduction of the corresponding benzenesulfonylchlorides. P-t-butylbenzenesulfonylchloride[24a], p-methoxybenzenesulfonyl-

chloride[24b], 2,4-dimethylbenzenesulfonylchloride [24c], 2,4,6-trimethylbenzenesulfonylchloride [24d,e] and 2,4-diisopropylbenzenesulfonylchloride[24f] were described in the literature.

General procedure for the synthesis of substituted benzenesulfonylchlorides; p-t-butylbenzenesulfonylchloride

To a stirred solution of 67 g (0.5 mol) of t-butylbenzene in 150 ml chloroform was carefully added at -5 to 0 °C over 30 min. 175 g (1.5 mol) of chlorosulfonic acid. The ice-salt bath was removed and the temperature allowed to approach room temperature during 1 h. with continuous stirring. The solution was poured onto chopped ice and the mixture transferred to a separatory funnel. The chloroform layer was separated and the aqueous layer extracted twice with 100 ml $CHCl_3$. The combined organic layers were washed with two portions of 100 ml ice-water, dried over anhydrous sodium sulphate and filtered. The chloroform was removed by rotatory evaporation to yield 107.5 g (0.46 mol) of crude p-t-butylbenzenesulfonylchloride, as a white solid after cooling to room temperature.

p-t-Butylbenzenesulfonylchloride

^{1}H NMR: 1.3 (s, 9H, H8, tBu.), 7.4 (d, 2H, J=8Hz, H3, H5), 7.8 (d, 2H, J=8Hz, H2, H6).

p-Methoxybenzenesulfonylchloride

On evaporating the chloroform, there remained a pale yellow oil which crystallized on cooling and scratching. The crystals were filtered and washed with n-hexane. Yield 67%, m.p. 39.9-41.8 °C (lit.[24b] m.p. 40-42 °C). ^{1}H NMR: 3.8 (s, 3H, OMe), 6.9 (d, 2H, J=10Hz, H3, H5), 7.8 (d, 2H, J=10Hz, H2, H6).

2,4-Dimethylbenzenesulfonylchloride

This sulfonylchloride remained a pale yellow oil and the crude product was used as such in the next step (yield 85%). ^{1}H NMR: 2.3 (s, 3H, H7), 2.7 (s, 3H, H8), 7 (m, 2H, H3, H5), 7.7 (d, 1H, J=9Hz, H6).

2,4,6-Trimethylbenzenesulfonylchloride

On evaporating the chloroform there remained a pale yellow oil, which crystallized upon cooling to room temperature. The crystals were filtered and washed with n-pentane. Yield 80%, m.p. 54.1-56.5 °C (lit.[24d,e] yield 65- 72%, m.p. 50-53 °C). ^{1}H NMR: 2.3 (s, 3H, H8), 2.7 (s, 6H, H7, H9), 6.9 (s, 2H, H3, H5).

2,4-Diisopropylbenzenesulfonylchloride

Obtained as a pale yellow oil in 100% yield. The crude sulfonylchloride was used for the next step.
^{1}H NMR: 1.2 (d, 6H, J=3.6Hz, H10), 1.4 (d, 6H, J=3.6Hz, H8), 2.9 (se, 1H, J=6Hz, H9), 4.0 (se, 1H, J=6Hz, H7), 7.0 (d, 1H, J=1.6Hz, H3), 7.3 (dd, 1H, J=8Hz, J=1.6Hz, H2), 8.0 (d, 1H, J=8Hz, H1).

General procedure for synthesis of arylthiols; p-t-butylthiophenol 4a

A 2 liter three-necked round bottomed flask was charged with 1.069 kg. crushed ice and 365 g concentrated sulfuric acid. The stirred mixture was cooled to -5 °C, and 107 g (0.46 mol) of t-butylbenzenesulfonylchloride was added, while remaining the temperature below 0 °C. Next 178 g zink-powder was gradually added and stirring continued for 1 h. at 0 °C. The flask was suited with a condensor and the mixture was gradually warmed to reflux temperature. After refluxing for 6 h., the p-t-butylthiophenol **4a** was isolated by means of steam distillation. The product was separated from water and the water

layer was extracted with two portions of 100 ml chloroform. The combined chloroform and product layers were dried over magnesium sulphate. After filtration, the chloroform was evaporated in vacuo and subsequently p-t-butylthiophenol **4a** was distilled.

p-t-Butylthiophenol 4a

Yield 69%, overall yield (from p-t-butylbenzene) 64%, b.p. 123-125 °C (2 mmHg) (lit.[24a] yield 81%, b.p. 120 °C (22 mmHg)). ^{1}H NMR: 1.3 (s, 9H, tBu.), 3.2 (s, 1H, SH), 7.1 (s, 4H, Ar).

p-Methoxythiophenol 4d

Yield 82%, overall yield (from anisol) 55%, b.p. 102.5-103.5°C (12 mmHg) (lit.[25d] b.p. 116.5-117.5 °C (25 mmHg)). ^{1}H NMR: 3.1 (s, 1H, SH), 3.7 (s, 3H, OMe), 6.6 (d, 2H, J=8Hz, H2, H6), 7.1 (d, 2H, J=8Hz, H3, H5).

2,4-Dimethylthiophenol 4e

Yield 69 %, overall yield (from 2,4-dimethylbenzene) 57%, b.p. 84.5-86 °C (10 mmHg) (lit.[25a] yield 48%, b.p. 127°C (50 mmHg)). ^{1}H NMR: 2.2 (s, 6H, H7, H8), 2.9 (s, 1H, SH), 8.3 (m, 3H, Ar).

2,4,6-Trimethylthiophenol 4f

Yield 47%, overall yield (from 2,4,6-trimethylbenzene) 35%, b.p. 94-95°C (8 mmHg) (lit.[25c] yield 66%, b.p. 109.5-111.5 °C (18 mmHg)). ^{1}H NMR: 2.1 (s, 3H, H8), 2.3 (s, 6H, H7, H9), 2.8 (s, 1H, SH), 6.7 (s, 2H, H3, H5).

2,4-Diisopropylthiophenol 4g

Overall yield (from 2,4-diisopropylbenzene) 68%, b.p. 78-81°C (1 mmHg) (lit.[25b] yield 18.8% , b.p. 80-85°C (1 mmHg)). ^{1}H NMR: 1.1 (d, 6H, J=1.8Hz, H10), 1.2 (d, 6H, J=1.8Hz, H8), 2.8 (se, 1H, J=7Hz, H9), 3.1 (s, 1H, SH), 3.2 (se, 1H, J=7Hz, H7), 6.9 (m, 3H, Ar).

General procedure for the standard reaction of 5-methoxy-2(5H)-furanone (2) and p-t-butylthiophenol (4a)

A stirred solution of 50 mg quinidine **10d** (0.15 mmol) and 0.947 g p-t-butylthiophenol **4a** (5.7 mmol) in 19.8 ml of dry toluene was cooled to -33 °C in a nitrogen atmosphere. Next 1 g (8.76 mmol) of 5-methoxy-2(5H)-furanone **2** was added. After 18 h. the thiol conversion was checked by means of GC-analysis. A sample for GC-analysis was kept at temperatures below -33 °C and an injection was done directly from this cold sample to prevent further conversion. The reaction mixture was worked-up, after complete thiol conversion, by evaporating the toluene in vacuo following by bulb-to-bulb distillation. 5-Methoxy-2(5H)-furanone **2** was distilled at 65 °C (1 mmHg). When flash-chromatography was used as a work-up procedure, the reaction mixture was added to a silica gel column (4x 10 cm) and eluted successively with pentane/ether (10:1), pentane/ether (3:1) and pure ether. The isolated 5-methoxy-2(5H)-furanone **2** was purified by means of bulb-to-bulb distillation at 65 °C (1 mmHg). The isolated thiol-addition product 5-methoxy-4-(p-t-butylphenylthio)-butyrolactone **3b** was distilled (bulb-to-bulb) at 165 °C (0.06 mmHg). In cases were 5-methoxy-2(5H)-furanone **2** was slowly added to the reaction mixture, the following procedure was used. A solution of 50 mg (0.15 mmol) quinidine **10d** and 0.947 g (5.7 mmol) p-t-butylthiophenol **4a** in 15.2 ml dry toluene was cooled to -33 °C under N_2-atmosphere. Next 1

g (8.76 mmol) 5-methoxy-2(5H)-furanone **2**, dissolved in 3.4 ml toluene was added dropwise over a 2.5 h. period of time, using a 5 ml syringe and a pump. The syringe was finally rinsed with 1 ml toluene. ^{1}H NMR (**3b**): 1.3 (s, 9H, tBu), 2.3-2.5 (dd, J=3Hz, H3'), 2.6-2.9 (dd, J=8Hz, H3), 3.4 (s, 3H, OCH3), 3.7 (m, 1H, H4), 5.1 (s, 1H, H5), 7.3 (s, 4H, Ar). ^{1}H NMR (**2**): 3.5 (s, 3H, OMe), 5,8 (s, 1H, H5), 6.2 (d, 1H, J=6Hz, H3), 7.2 (d, 1H, J=6Hz, H4). ^{13}C NMR (**2**): 56.57 (q, C6), 103.77 (d, C5), 124.64 (d, C3), 150.06 (d, C4), 170.04 (s, C2).

Determination of the enantiomeric excess of 2

To a solution of 26 mg (0.23 mmol) 5-(R,S)-methoxy-2(5H)-furanone **2** in 0.53 ml DMF, was added 42 mg (0.35 mmol) (l)-α-methylbenzylamine (1.5 equiv.). After stirring for 5 min., the homogeneous reaction mixture was allowed to stand for 20 h. at room temperature. Next the solvent and the excess (l)-α-methylbenzylamine were evaporated (65 °C, 1 mmHg) to afford the amine adduct **5** (mixture of diastereoisomers) as an oil. From the integrations of the absorptions at 4.9 and 5.2 ppm (the absorptions for the acetal-protons), the e.e. was calculated.

4-(R,S)-((S)-α-methylbenzylamino)-5-(R,S)-methoxybutyrolactone (5)

^{1}H NMR: 1.4 (d, 3H, J=7Hz, H7), 1.7 (br s, 1H, NH), 2.2 and 2.4 (dd, 1H, J=14Hz, 4Hz, H3'), 2.6 and 2.9 (dd, 1H, J=14Hz, 8Hz, H3), 3.3 (m, 1H, H4), 3.3 and 3.5 (s, 3H, OCH3), 3.7 and 3.8 (dq, 1H, J=10Hz, 3Hz, H6) 4.9 and 5.2 (s, 1H, H5), 7.0-7.4 (m, 5H, Ar).

4-(R)-((S)-α-methylbenzylamino)-5(R)-methoxybutyrolactone

^{1}H NMR: 1.34 (d, 3H, J=7Hz, H7), 1.5 (s, br, 1H, NH), 2.32 (dd, 1H, J=14Hz, J=4Hz, H3'), 2.72 (dd, 1H, J=14Hz, 8Hz, H3), 3.24 (m, 1H, H4), 3.28 (s, 3H, OCH_3) 3.76 (q, 1H, J=3Hz, H6), 4.86 (s, 1H, H5), 7.0-7.4 (m, 5H, Ar).

Determination of the optical purity of R-2a

To a solution of 129 mg (1.13 mmol) (R)-5-methoxy-2(5H)-furanone **2a** in 6 ml dichloromethane was added 0.156 g (1.42 mmol) thiophenol **4b**. This solution was cooled to 0 °C and 25 mg triethylamine in 1.5 ml dichloromethane was added. After stirring for 15 min. at 0 °C and 1 h. at room temperature, the conversion of (R)-5-methoxy-2(5H)-furanone **2a** was checked by means of GC-analysis. The conversion turned out to be complete. Next the solvent, triethylamine and excess thiophenol were evaporated in vacuo (50 °C, 1 mmHg) to afford pure 5-methoxy-4-(phenylthio)-butyrolactone **3c** as an oil. 5-Methoxy-4-(phenylthio)-butyrolactone **3c** was dissolved in 15 ml dry THF. This solution was added dropwise to a solution of 4 mmol lithium aluminium hydride in 14 ml THF at 0 °C under a nitrogen atmosphere. The solution was stirred for 1 h. at 0 °C and for 12 h. at room temperature. The excess lithium aluminium hydride was destroyed by adding 1.5 ml water and next 1.5 ml 10% potassium hydroxide solution. The resulting salts were filtered and washed with ether (3x 40 ml). The combined ether/THF layers were dried over anhydrous sodium sulphate, filtered and evaporated in vacuo. The residue was purified by bulb-to-bulb distillation, giving 160 mg (71%) of 2-phenylthio-1,4-butanediol **(6)**, b.p. 165 °C (0.05 mmHg) (lit.[7c] 160°C, 0.1 mmHg) as a colourless oil, $[\alpha]^{20}_D$= + 22.5° (c 3.2, MeOH). ^{1}H NMR: 1.4-2.0 (m, 2H, H2), 2.3-3.0 (s, br, 2H, OH), 3.0-3.4 (m, 1H, H3), 3.4-3.8 (m, 4H, H1, H4), 7.0-7.3 (m, 5H, Ar) Lit.[7c,13]: $[\alpha]^{20}_D$= +40.2° (c 3.5, MeOH) for optically pure (R)-**6** and $[\alpha]^{20}_D$= -32.6° (c 3.5, MeOH) for (S)-2-phenylthio-1,4-butanediol **6** with an optical purity of 81%.

General procedure for kinetic measurements

A solution of 0.290 g (2.54 mmol) 5-methoxy-2(5H)-furanone **2** and 0.278 g (1.67 mmol) p-t-butylthiophenol **4a** in 3.270 g (3.76 ml) toluene was placed in a thermostated bath, in order to reach the reaction temperature. From a stock solution of the catalyst (quinidine **10d**), kept at the reaction temperature, 2.0 ml was added to the solution of the reactants. The resulting mixture was shaken well for about 30 seconds. The polarimeter cell was filled with this solution in a period as short as possible, and the rotation measurements were started. The rotation was measured with time intervals of 10 or 15 seconds. In order to maintain a constant reaction temperature, the jacketed polarimeter cell was connected to a thermostated bath. The stock-solution of the catalyst contained 3.637 mg/ml quinidine **10d** in toluene, which resulted in 0.5 mol% of the catalyst in the reaction mixture.

Asymmetric synthesis of 4-phenylthiobutyrolactone

A stirred solution of 50 mg (0.15 mmol) quinidine **10d** and 1.019 g (9.3 mmol) thiophenol **4b** in 19.8 ml of dry toluene was cooled to -33 °C in a nitrogen atmosphere. Next 0.736 g (8.76 mmol) 2(5H)-furanone **9** was added. After 24 h. at -33 °C the thiol conversion turned out to be complete. The reaction mixture was allowed to reach room temperature and next filtered through a silica gel column (1.5 x 5 cm) and eluted with ether. The crude 4-phenylthiobutyrolactone was purified by means of bulb-to-bulb distillation (60°C, 0.03 mmHg) to yield 1.1 g (63%) 4-phenylthiobutyrolactone as an oil, $[\alpha]^{21}_{D}$= -5.6° (c 1, $CHCl_3$). ^{1}H NMR: 2.7 (m, 2H, H3), 4.2 (m, 3H, H4, H5), 7.3 (s, 5H, Ar).

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(*Received in UK* 6 *December* 1993; *revised* 31 *January* 1994; *accepted* 4 *February* 1994)