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SYNTHESIS AND DETERMINATION OF ENANTIOMERIC EXCESSES OF NON-RACEMIC TERT-THIOLS DERIVED FROM CHIRAL SECONDARY α-MERCAPTOCARBOXYLIC ACIDS.#

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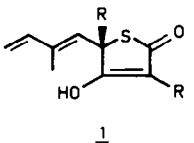
ABSTRACT. The optically active α-mercapto derivatives of propanoic, 3-phenylpropanoic, 2-phenylacetic, 3-methylbutanoic, 4-methylpentanoic, and (S)-3-methylpentanoic acids have been prepared. Condensation of these acids with pivalaldehyde gives 2-t-butyl-5-substituted-1,3-oxathiolanones (6); the cis geometric isomers are formed in excess and are obtained pure by crystallization. For the 5-benzyl derivative (6b) the cis arrangement for the major diastereomer was established by X-ray crystallography. These cis-disubstituted heterocycles (6), after deprotonation with lithium diisopropylamide (LDA) or lithium hexamethyldisilazide (LHMDS) and subsequent reaction with electrophiles such as alkyl halides, aldehydes, or ketones, furnish, after hydrolysis, in high enantiomeric excesses α-branched α-mercaptocarboxylic acids or esters (9). These result from an overall substitution of the proton in the α-position to the carbonyl group with retention of configuration and without racemization. This stereochemical course was established by a crystal structure determination of (2S)-8e obtained by benzylation of the enolate derived from cis-5-phenyl-1,3-oxathiolan-4-one (6c). The tert-α-mercaptocarboxylic acids are obtained optically active without employment of a chiral auxiliary. Their enantiomeric excesses were determined by esterification, conversion to diastereomeric phosphonodithioates on reaction with CH_3POCl_2, followed by integration of the well separated proton-decoupled ^{31}P-NMR signals. This is apparently the first example of enantiomeric excess determinations of chiral tertiary thiols.

Introduction

Interest in non-racemic chiral compounds with quaternary[1] carbon atoms like α-alkyl-α-hydroxycarboxylic acids[2a-e], -aldehydes,[2b] and -glycols,[2b] as well as α-dialkyl-β-hydroxycarboxylic acids[3] and α-alkyl-α-amino acids[4a,b] has been awakened as result of their biochemical activity and potential usefulness as chiral units in syntheses of natural products.[5] The effectiveness of α-alkyl-α-amino acids as inhibitors of amino acid decarboxylases deserves extra emphasis in this regard.[4b] Rational, enantioselective syntheses of reasonable generality for such quaternary centers present, however, a real challenge. This is even truer for non-racemic α-substituted-α-mercaptoacid derivatives for which, to our knowledge, no systematic syntheses have been devised.[6] Reports of the identification of these quaternary carbon bearing structural units in various natural products indicate the importance also of this class. For example, the recently discovered thiolactomycine antibiotics (1a,b) possess a previously undescribed and unique tertiary thiolactone structure.[8] The same units are found in gliotoxin (2), which can be viewed as an oxidative condensation product of two α-mercapto-α-amino acids as represented in 3.[9a] This latter

Dedicated to Professor Hans Wynberg on the occasion of his sixty-fifth birthday.

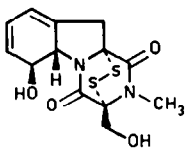
combination of functional groups, schematically illustrated in 4, is unstable, however, and has been found only in the form of acylated derivatives.[9b] Non-racemic tertiary thiols, like their secondary counterparts, may well be expected to exhibit biological activity.[10]



1

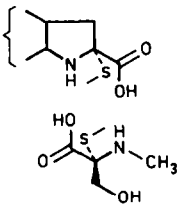
a) R = CH_3, thiolactomycin

b) R = C_2H_5, thiotetromycin

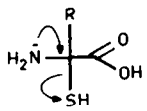


2

gliotoxin



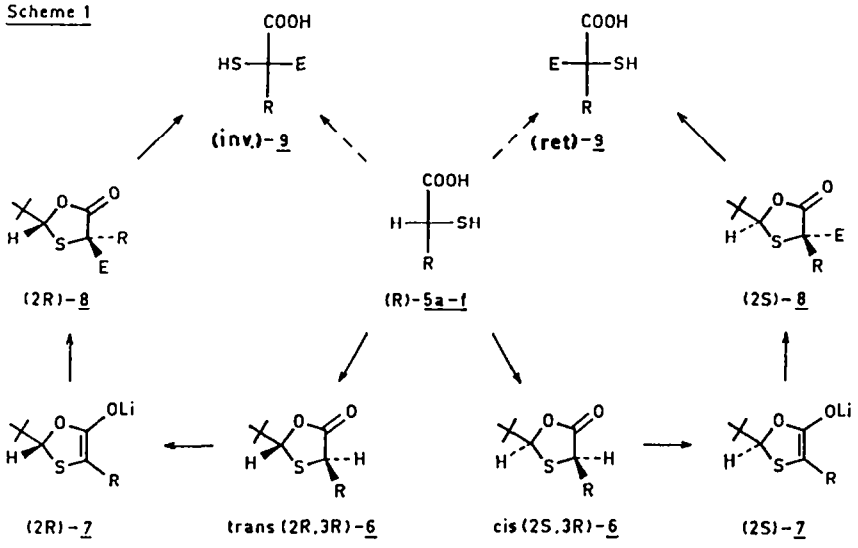
3



4

As part of our investigations on the synthesis[11] and enantiomeric excess (ee) determination[12] of non-racemic thiols we have now prepared several examples by stereospecific α-alkylation of chiral secondary thiols. The principle employed has been developed by Seebach and co-workers[2a] for α-hydroxy carboxylic acids and has been applied for one racemic α-mercaptocarboxylic acid. The approach, as applied to α-mercaptoacids (5), is outlined in Scheme 1. These are converted by reaction with pivalaldehyde to mixtures of cis and trans 1,3-oxathiolan-4-ones (6),[13,14] which are separated by fractional crystallization.[2a] An enolate is then generated with loss of the original asymmetric center. Attack of an electrophile on this enolate proceeds nearly exclusively trans to the tert-butyl group with regeneration of the asymmetric centra with predictable configuration in product (8). After hydrolysis an enantiomerically pure or enriched tertiary α-mercaptocarboxylic acid (9) is formed, either with overall retention (starting from cis-6) or inversion (from trans-6) of configuration. In principle both the (S) and (R) enantiomers of 9 can be obtained from a single enantiomer of (R)-5, if both the cis and trans acetals from 5 can be obtained selectively. The same rationale holds, of course, if one can start from the (S)-enantiomer of 5.

Scheme 1



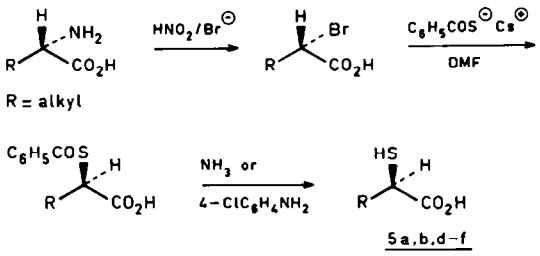
In this paper examples are described of application of this methodology to non-racemic α-mercaptocarboxylic acids. The determination of ee of the tertiary thiols formed is also described.

RESULTS AND DISCUSSION

A. Preparation and ee determination of chiral α-mercaptocarboxylic acids (5).

Five non-racemic (R) α-mercaptocarboxylic acids (5) were prepared from the corresponding α-bromocarboxylic acids, obtained by diazotization of the corresponding α-amino acids, by nucleophilic substitution with cesium thiobenzoate in dimethylformamide (DMF) and subsequent aminolysis (Scheme 2) as recently described by us.[11] Optically active (R)-thiomandelic acid (5c) was prepared by acid hydrolysis of optically pure (R)-2-acetylthio-2-phenyl acetic acid as described for the S enantiomer.[11] The enantiomeric excesses (ee) of the α-mercaptocarboxylic acids

Scheme 2



5a,b,d-f

(5) were determined after esterification with diazomethane, by application of the ^{31}P NMR method employing the non-chiral derivatizing agent CH_3POCl_2 recently described by us.[12] Yields and ee's are summarized in Table 1.

Table 1

Yields and Enantiomeric Excess for (R) α-Mercapto Carboxylic Acids (5)

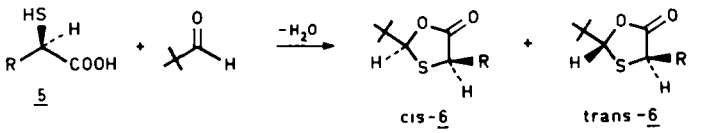
Compounds	R	Overall yield[a] (%)	e.e.[b]
5a	CH_3	64	≥ 98
5b	$C_6H_5CH_2$	61	92[c]
5c	C_6H_5	85	93[d]
5d	$(CH_3)_2CH$	67	≥ 98
5e	$(CH_3)_2CHCH_2$	78	81[c]
5f	$(S)CH_3CH_2CH(CH_3)$	64	≥ 98

a) Yield of pure, isolated material. b) This is the ee of the corresponding methyl ester, determined by the ^{31}P-method.[12] c. Starting material, the α-bromocarboxylic acid, was not optically pure, see Experimental and ref. 11. d. This compound is obtained from optically pure (R)-2-acetylthio-2-phenyl acetic acid by acid hydrolysis, which causes some racemization as described for the S-enantiomer.[11]

B. Preparation of the oxathiolanones. Configurational assignments.

Acid catalyzed acetalization of the (R)-α-mercaptocarboxylic acids (5a-f) with pivalaldehyde, with azeotropic removal of the water formed, leads to cis/trans mixtures of the oxathiolanones (6) as shown in Scheme 3.[2a] Except for 6d it was possible to separate the cis/trans isomers by crystallization. The remaining mother liquors can be hydrolyzed back to the starting materials, which can be recycled. By repeating this process, all of the material can, in principle, be converted to the (major) cis-isomer, if desired. The cis configuration of the major diastereomer

Scheme 3



6	R	yield (%)	cis/trans
a	CH_3	92	2.5 : 1
b	$C_6H_5CH_2$	78	2 : 1
c	C_6H_5	81	8 : 1
d	$(CH_3)_2CH$	50	3 : 1
e	$(CH_3)_2CHCH_2$	55	4 : 1
f	(S) $CH_3CH_2CH(CH_3)$	61	4.5 : 1

was determined unambiguously for the case of oxathiolanone 6b by an X-ray crystallographic determination. The structure is illustrated in Fig 1. For a discussion of the crystallographic data see below. The configurations of the major isomers of 6a-f were assigned as cis in

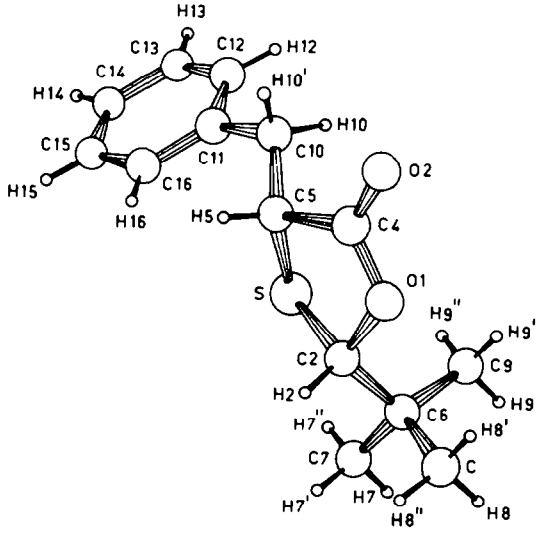


Fig. 1. Structure of cis-6b as determined by X-ray structural analysis. Note the unambiguously cis-arrangement of H2,H5. The atomic coordinates and thermal parameters for structure 6b and 8e (Figs. 3, 4) are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by a full literature citation for this paper. Please note that the crystallographic numbering differs from that used in this article.

analogy with 6b, by comparisons with published ^{1}H NMR data for dioxolanones and oxathiolanones[2a,14] and by comparison of the results of alkylations of the enolates (7) with the results obtained by Seebach[2a] for the analogous 1,3-dioxolan-4-ones.

C. Discussion of the X-ray crystallographic data for cis-6b.

From Fig 1 the cis orientation of the substituents at C-2 and C-4 is crystal-clear. The cis-isomer is clearly more stable than the trans compound, because in the puckered envelope

conformation adopted the steric interactions of the substituents with the ring are minimalized. Noteworthy is the envelope structure of the 5-ring, with the sulfur atom bending out of the plane through C2, O1, C4, and C5, the nearly eclipsed conformation of H2 and H5, and the deviation in the angles between C5-C4-O2 (125°) and C5-C4-O1 (114°) from the expected value (120°) for an sp^2 carbonyl carbon atom. A stereo-view of cis-6b in the unit cell is given in Fig 2. Important bond-distances and bond-angles are summarized in Table 2.

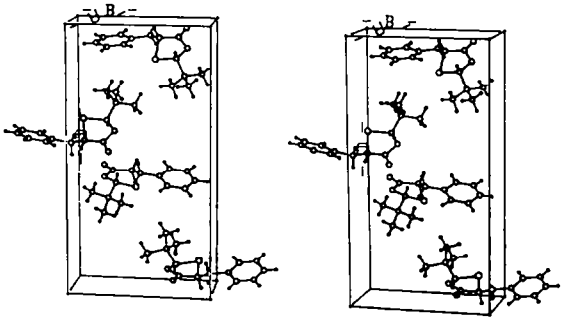


Fig. 2. Stereo-view of the packing of 6b in the unit cell.

Table 2. Most Important Bond Distances and Bond Angles for cis 6b

Bond Distances (A)			Bond Angles in Degrees			
Atom 1	Atom 2	Distance[a]	Atom 1	Atom 2	Atom 3	Angle
S	C2	1.829(2)	C2	S	C5	90.0(2)
S	C5	1.822(6)	C2	O1	C4	115.7(4)
O1	C2	1.444(5)	O1	C2	C6	110.3(4)
O1	C4	1.349(8)	C4	C5	C8	112.3(6)
O2	C4	1.188(9)	O1	C4	O2	120.9(6)
C2	C6	1.510(7)	O1	C4	C5	113.6(6)
C4	C5	1.508(9)	O2	C4	C5	125.5(6)
C5	C10	1.498(10)	C2	C6	C8	109.1(5)
C6	C8	1.535(11)	C8	C6	C9	108.6(7)
C10	C11	1.521(9)	C5	C10	C11	115.7(6)
			C10	C11	C16	121.7(6)

a. Numbers in parentheses are estimated standard deviations in the least significant digits.

D. Alkylation of the enolates 7 with alkyl halides. Proof of overall retention of configuration on alkylation.

The cis-oxathiolanones (6a-c,e,f) were deprotonated with LDA or LHMDS (in the case of 6b) at -80°C by adding the solution of the base in THF/hexane (1:2) to a solution of 6 in THF. The 3:1 cis/trans mixture of 6d was benzylated to give a 85% yield of a 3:1 mixture of diastereomers, which could not be separated by crystallization. Primary alkyl and benzyl bromides and iodides were used to alkylate the enolates 7a-c,e,f, (alkylation of the enolate from racemic 6a with allyl bromide has been described)[2a] to give the 2,5-disubstituted oxathiolanones (2S)-8 as shown in Table 3. As can be seen yields are good to high.[15] The diastereoselectivities are mostly above 95% as determined by ^1H and/or ^{13}C NMR spectroscopy. Entries 9 and 10 show cases of asymmetric synthesis wherein the asymmetric induction is influenced also by the second chiral center in the 5-alkyl side chain. The lower diastereoselectivity (ds) of 60% for entry 9 is in this light not surprising. The >95% ds for entry 10, obtained for the larger (than methyl) benzyl electrophile (entry 9) is a pleasing result. The only appreciable "miscarriage" is the result found in entry 6. Methylation of the enolate from cis 6b and LDA afforded (2R)-8 with a ds of only 86%. The use of LHMDS led to

no improvement in the ds. We have no explanation for the formation of appreciable quantities of the unanticipated diastereomer in this case.

Table 3. Alkylations of Enolate 7 with Alkyl Halides.

(2S)-7 (2S)-8

Entry	8	R^1	R^2	(halide used)	yield (%)[a]	ds (%)[b]
1	a	CH_3	C_2H_5	(I)	60	> 95
2	b	CH_3	$C_6H_5CH_2$	(Br)	78	> 95
3	c	CH_3	$CH_2CH=CH_2$	(Br)	92	> 95
4	d	C_6H_5	CH_3	(I)	82	> 95
5	e	C_6H_5	$C_6H_5CH_2$	(Br)	68	> 95
6	f	$C_6H_5CH_2$	CH_3	(I)	70	86[c]
7	g	$(CH_3)_2CHCH_2$	CH_3	(I)	59	> 95
8	h	$(CH_3)_2CHCH_2$	$C_6H_5CH_2$	(Br)	76	> 95
9	i	(S) $CH_3CH_2CH(CH_3)$	CH_3	(I)	85	60[d]
10	j	(S) $CH_3CH_2CH(CH_3)$	$C_6H_5CH_2$	(Br)	90	> 95[d]

a) Yields of chromatographed or distilled materials, b) A diastereoselectivity of >95% means that no other diastereomer could be detected by 200 MHz ^{1}H NMR and/or by 50.311 MHz ^{13}C NMR. The experiment listed in entry 3 is for the racemic compound.[2a] c) The reason for the lower ds in this case is not known. The use of LHMDS as a base had no influence on the ds. d) See text for comment on this result.

The postulated steric course of these reactions, alkylation with retention of configuration starting from cis-6, is supported by an X-ray crystallographic determination of the structure of (2S)-8e (Figs 3 and 4).The crystallographic data are discussed in the following section. The benzylated compounds (8b,e,h,j) all showed a remarkably large upfield shift (1.2 to 1.7 ppm) in the ^{1}H NMR for the C-2 hydrogen as compared to the starting materials (6). From CPK models a folded conformation was expected, with the benzyl group bent back under the heterocyclic ring, the C-2 acetal hydrogen coming close to the ring and pointing nearly to the middle of that ring, causing a shielding effect on the C-2 hydrogen.

Another phenomenon in the ^{1}H NMR spectrum of 8e,d is that the ring hydrogens of the phenyl group are spread over an unusually wide range (about 0.4 ppm) for a monosubstituted aromatic ring.[16] This appears to be the result of a hindered rotation of the phenyl group, causing all of its hydrogens to become nonequivalent on the NMR time scale. Attempts to overcome the hindered rotation by raising the temperature had no observable effect. Samples of 8e,d in DMSO-d_6 could be heated to 160°C without any sharpening of the phenyl absorptions.

Fig. 3. Structure of 8e determined by X-ray crystallography (see also footnote to Fig. 1).

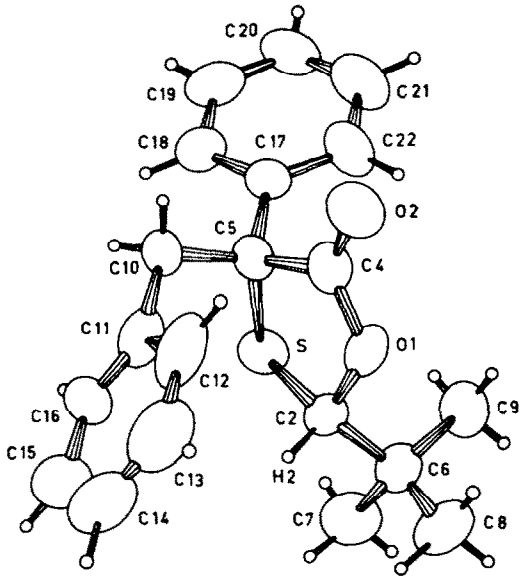
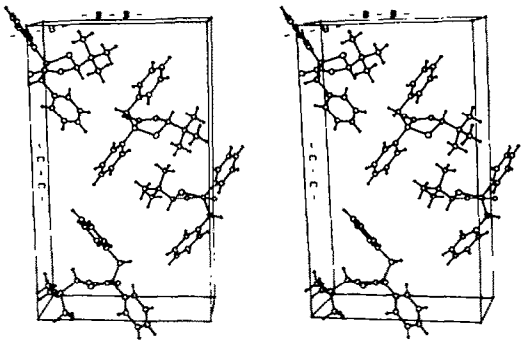


Fig. 4. Stereoscopic view of 8e in the unit cell.



E. Discussion of the X-ray crystallographic data for 8e.

From Figs 3 and 4 it is clear that the alkylations of the enolate (2S)-7 derived from the (major) cis isomer (6) take place with retention of configuration. The benzyl group is indeed folded back under the thiolactone ring, coming close (2.92 Å) to the acetal hydrogen H-2 as expected from CPK models. The large upfield shift of H-2 (1.4 ppm) as compared to 6c can be explained beautifully by the shielding effect of the aromatic ring. Extreme crowding leading to hindered rotation of the C-5 bonded phenyl group is obvious. Furthermore, the O1-C4-C5 (114.6°) and O2-C4-C5 (124.1°) bond angles deviate from the theoretically expected value for the sp^2

carbonyl carbon (120°). The fact that these compounds are so difficult to hydrolyze (see further) can be readily anticipated from the steric hindrance so clear from the structural data. The ORTEP drawing of 8e (Fig 3) also indicates the low thermal mobility of the phenyl ring (C17-C22), especially for atoms C18 and C22 (for details see Table 5). Bond angles and lengths of special interest are compiled in Table 4.

Table 4. Most Important Bond Distances and Bond Angles for 8e

Bond Distances (Å)			Bond Angles in Degrees			
Atom 1	Atom 2	Distance[a]	Atom 1	Atom 2	Atom 3	Angle[a]
S	C2	1.821(1)	C2	S	C5	92.3(1)
S	C5	1.825(4)	C2	O1	C4	116.7(3)
O1	C2	1.443(3)	O1	C2	C6	109.4(2)
O1	C4	1.341(5)	C4	C5	C10	106.9(3)
O2	C4	1.197(5)	C4	C5	C17	111.2(3)
C2	C6	1.524(4)	C10	C5	C17	112.9(3)
C4	C5	1.531(6)	O1	C4	O2	121.2(4)
C5	C10	1.555(5)	O1	C4	C5	114.6(3)
C5	C17	1.533(5)	O2	C4	C5	124.1(4)
C10	C11	1.517(6)	C2	C6	C8	107.2(4)
C6	C9	1.528(7)	C8	C6	C9	108.3(4)
			C5	C17	C22	121.6(4)
			C10	C11	C12	121.6(4)

a. Numbers in parentheses are estimated standard deviations in the least significant digits.

Table 5. Positional Parameters and Their Estimated Standard Deviations for 8e.

Atom	x	y	z	B(A2)
S	0.3326	0.1885	0.1131	3.87(2)
O1	0.1686(4)	0.1705(2)	0.1574(1)	4.28(6)
O2	0.1154(5)	0.0028(2)	0.1615(1)	4.75(7)
C2	0.3287(2)	0.24895(6)	0.15094(5)	3.83(9)
C4	0.2336(6)	0.0729(3)	0.1520(2)	3.63(8)
C5	0.4689(6)	0.0605(3)	0.1363(2)	3.27(8)
C6	0.2364(7)	0.3394(3)	0.1161(2)	4.7(1)
C7	0.063(1)	0.3890(4)	0.1555(3)	7.1(1)
C8	0.416(1)	0.4148(4)	0.1048(3)	7.2(1)
C9	0.1356(9)	0.3062(4)	0.0565(2)	6.1(1)
C10	0.5816(7)	0.0210(3)	0.1943(2)	3.81(9)
C11	0.5619(7)	0.0929(3)	0.2479(2)	4.00(9)
C12	0.3818(8)	0.0938(4)	0.2835(2)	5.3(1)
C13	0.367(1)	0.1614(5)	0.3308(2)	7.0(1)
C14	0.528(1)	0.2266(4)	0.3441(2)	7.8(2)
C15	0.710(1)	0.2264(4)	0.3090(2)	7.0(2)
C16	0.7245(8)	0.1588(4)	0.2616(2)	5.0(1)
C17	0.4991(6)	-0.0111(3)	0.0821(2)	3.54(8)
C18	0.6945(7)	-0.0551(3)	0.0709(2)	4.3(1)
C19	0.7259(8)	-0.1165(4)	0.0207(2)	5.6(1)
C20	0.564(1)	-0.1336(4)	-0.0186(2)	5.8(1)
C21	0.3702(9)	-0.0898(4)	-0.0083(2)	6.3(1)
C22	0.3387(8)	-0.0271(4)	0.0404(2)	5.2(1)

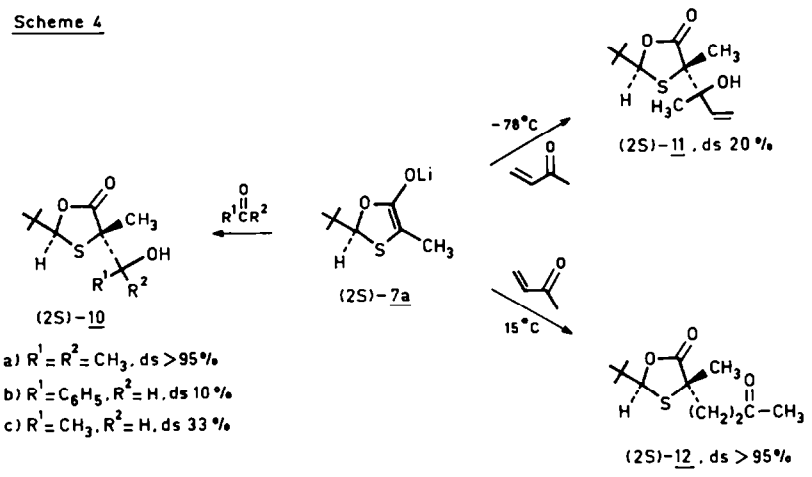
F. Reactions of the enolate (2S)-7 with aldehydes and ketones and an α,β-unsaturated ketone.

Addition to carbonyl groups (see Scheme 4) of the enolate (2S)-7a derived from cis-6a did not give such straightforward results as for the alkylations. Although the desired products (2S)-10 could be obtained by chromotography in 40-85% yields (see Scheme 4), byproduct formation was substantial.[17] The diastereoselectivities at C5 are >95% but the induction at the newly formed third chiral center (C1') in the case of aldehydes [(2S)-10b,c] and unsymmetrical ketones [(2S)-11] is, however, low (10-30% ds).

With the α,β-unsaturated ketone, methylvinylketone, complete selectivity for either 1,2-addition (at -78°C leading to 11) or 1,4-addition (at 15°C leading to 12) could be obtained with

enolate (2S)-7; either (2S)-11 or (2S)-12 can be obtained selectively depending on the conditions used.[6a]

Scheme 4



G. Hydrolysis of the 2,5-disubstituted oxathiolanones. Determination of ee of the tertiary thiols formed.

Some of the 2,5-disubstituted oxathiolanones (2S)-8 were hydrolyzed or transesterified to the tertiary α-mercaptocarboxylic acids or esters (S)-9. Acid hydrolysis (CH_3OH/6N HCl 2:1) of 8b,f was slow. Several days at reflux temperature were required to obtain complete hydrolysis to the acids. Details are described in the Experimental Section. Compound 8j was resistant to these conditions. After one week at reflux temperature only starting material was found. Basic hydrolysis (CH_3OH/LiOH), however, afforded the acid (9f). Transacetalization (CH_3OH saturated with dry HCl) proceeded somewhat easier. After two to three days at reflux temperature the tertiary α-mercaptocarboxylic esters (9a,d,e) were obtained in 80-95% yields. This is to our knowledge the first systematic synthesis of non-racemic tertiary thiols.

The ee's of these thiols were determined on the methyl esters of 9 by reaction with CH_3POCl_2 in the presence of triethyl amine followed by measurement of the meso/d,l ratios by integration of the ^{31}P NMR absorptions as described by us previously.[12,18] This is the first application of this method to tertiary compounds and the first ee determination of tertiary thiols. Although the splittings between the diastereomeric phosphonates derived from tertiary thiols were less than those with the secondary compounds,[19] base-line separation was obtained in all cases. Results are summarized in Table 6. From this Table it can be seen that the high ee's of 9 are in excellent agreement with the high diastereoselectivities of the alkylation (see also Table 3).

It can be concluded that the α-alkylation method described here provides a good route to the synthesis of chiral tertiary thiols of high ee. Applications of this methodology are under investigation.

Table 6. Enantiomeric Excess Determinations of Tertiary Thiols 9 $R^1R^2C(SH)CO_2R^3$

Starting Material (% ee)		Product (S)-9 R^1	R^2	R^3	% ee-9[a]
5a	(>98)	9a CH_3	C_2H_5	CH_3	>95
5a	(>98)	9b CH_3	$CH_2C_6H_5$	H	>95
5b	(92)	9d $CH_2C_6H_5$	CH_3	H	77[b]
5c	(92)	9c C_6H_5	CH_3	CH_3	91
5e	(82)	9e $(CH_3)_2CHCH_2$	$C_6H_5CH_2$	CH_3	78
5f	(>98)	9f (S)$C_2H_5CH(CH_3)$	$C_6H_5CH_2$	H	>95

a) The ee's of 9 were determined on the methyl esters (R^3=CH_3). b) The diastereoselectivity of alkylation was in this case 86%, see Table 3.

Acknowledgement. We are grateful to Dr. B. Feringa of this department for cooperation in the development of the method for ee determinations used here and to Mr. F. van Bolhuis of the departmental crystallographic center for determination of the X-ray structures.

Experimental Section

General remarks. All solvents and reagents were purified and dried where necessary according to standard procedures. Melting points (uncorrected) were determined on a Mettler FP-2 melting point apparatus, equipped with a Mettler FP-21 microscope. Infrared spectra were recorded on a Perkin-Elmer 257 grating spectrometer. ^1H NMR spectra were recorded in $CDCl_3$ on a Hitachi Perkin Elmer R-24B NMR spectrometer (at 60 MHz) or on a Nicolet NT-200 spectrometer (at 200 MHz). Chemical shifts in ^1H NMR are denoted in δ units (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard at δ = 0. ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian XL-100 (at 25.16 MHz) or on a Nicolet NT200 (at 50.32 MHz) spectrometer. Chemical shifts are denoted in δ units (ppm) relative to δ_{CDCl_3} = 76.9. ^{31}P NMR spectra were recorded on a Nicolet NT-200 (at 81.0 MHz) spectrometer; chemical shifts were determined relative to 85% H_3PO_4 (δ = 0.0) as an external standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. Elemental analyses were performed in the microanalytical department of this laboratory. The diastereomeric composition (% ds = diastereoselectivity) of products was determined by ^1H and/or ^{13}C NMR.

Optical rotations were determined with a Perkin-Elmer Model 241 Polarimeter. The ee's of starting materials, intermediates and products were determined as described before.[11] The ee's of tertiary thiols were determined by the ^{31}P method recently described by us.[12] All reactions involving lithium derivatives were carried out in an atmosphere of oxygen-free, dry nitrogen.

Acetalization of α-mercaptocarboxylic acids. We used the procedure as described by Seebach.[2a] General procedure: a mixture of 0.5 mol of carboxylic acid, 1 mol of pivalaldehyde, 1 g of p-toluenesulfonic acid, 2 drops of conc. H_2SO_4 and 400 ml of pentane was refluxed with azeotropic removal of the water formed (one night). The resulting solution was washed with water (2 x 200 ml), dried ($MgSO_4$), and concentrated at reduced pressure.

General procedure for reactions of the enolate from the oxathiolanone (6) with various electrophiles. A 10 mmol run is described. Unless otherwise noted, a solution of 10 mmol of 6 in 60 ml THF was cooled to -80° and 10.5 ml of a 1M LDA solution (THF-hexane 1:2) was added. After stirring for 30 min at -80°C, the electrophile was added and the temperature was allowed to warm to -20°C over a period of 3 hours. The reactionrsolution was poured into 100 ml of half-sauurated ammonium chloride solution and extracted twice with 100 ml of ether. The organic layer was dried over $MgSO_4$ and the solvent removed in vacuo. Specific details are given for each compound.

(R)-2-Mercaptopropanoic acid (5a) was prepared as described[11] except that (S)-2-chloropropanoic acid was used instead of (S)-2-bromopropanoic acid. The compound has $[\alpha]_D^{23}$ 56.4° (c 4, EtOAc), ee > 98% (^{31}P method).

(R)-2-Mercapto-3-phenylpropanoic acid (5b) was prepared as described.[11] $[\alpha]_D^{20}$ -9.5 (c 1, MeOH), ee 92% (^{31}P method).

(R)-2-Mercapto-2-phenylacetic acid (R-thiomandelic acid) (5c) was prepared as described[11] for the S-enantiomer. $[\alpha]_D^{25}$ -120° (c 2, 95% EtOH), ee 92% (^{31}P method).

R-2-Mercapto-3-methylbutanoic acid (5d) was prepared as described.[11] $[\alpha]_D^{20}$ +23.3° (c 0.68, ether), ee >98% (^{31}P method).

(R)-2-Mercapto-4-methylpentanoic acid (5e). (R)-(2-Benzoylthio)-4-methylpentanoic acid was prepared by treatment of (S)-2-bromo-4-methylpentanoic acid, $[\alpha]_D^{20}$ +38.1° (c 2, MeOH) (lit.[20] $[\alpha]_D^{22}$ +38.2° (c 2, MeOH)) (39.0 g, 200 mmol) with $CsSCOC_6H_5$ (56.8 g, 210 mmol) in 350 ml DMF to give the thiobenzoate as a thick oil, 46.9 g (192 mmol, 96% yield), which was essentially pure by ^{1}H and ^{13}C NMR; $[\alpha]_{578}^{20}$ +73.3° (c 3, $CHCl_3$); ^{1}H NMR: δ 0.8-1.2 (dd, 6H), 1.4-2.2 (m, 3H), 4.5 (t, 1H), 7.3-8.2 (m, 5H) and 11.5 (s, 1H); ^{13}C NMR: δ 190.02 (s), 178.15 (s) [133.69 (s), 130.02 (d), 128.54 (d), 127.26 (d) Ph] 44.08 (d), 39.96 (d), 25.98 (t), 22.12 (q) and 21.94 (q); exact mass calcd for $C_{13}H_{16}O_3S$ 252.082, found 252.081. Treatment of the thiobenzoate (100 mmol, 25.2 g) with 1N NH_3 (400 ml) gave the crude acid 5e (12.0 g, 81 mmol, 81% yield). For analytical purposes a sample was purified by chromatography (CH_2Cl_2, silica gel 60, Rf ~0.1) and distillation, bp 70°C/0.01 Torr; $[\alpha]_{578}^{22}$ +25.1° (c 1, $CHCl_3$) [literature:[20] $[\alpha]_D^{20}$ -23.8° (c 1.8, ether) for the S-enantiomer]; ^{1}H NMR: δ 0.8-1.0 (dd, 6H), 2.0-1.3 (m, 3H), 2.05 (d, 1H, 3H), 3.1-3.6 (m, 1H) and 11.8 (s, 1H); ^{13}C NMR: δ 179.60 (s) [133.61 (s), 132.26 (d), 128.28 (d), 127.32 (d)] 43.86 (d), 38.93 (d), 25.87 (t), 21.96 (q), 21.87 (q); Anal. calcd for $C_6H_{12}O_2S$:C 48.62, H 8.16, S 21.63; found: C 48.25, H 8.08, S 21.18; exact mass calcd for $C_6H_{12}O_2S$: 148.056, found 148.058. The methylester prepared for this sample had an ee of 82% as determined by the ^{31}P method.

(R)-2-Mercapto-(S)-3-methylpentanoic acid (5f). (R)-(2-Benzoylthio) (S)-3-methylpentanoic acid was prepared by treatment of (S)-2-bromo-(S)-3-methylpentanoic acid; $[\alpha]_D^{20}$24.2 (c 2, benzene) (lit.[21] $[\alpha]_D$ +24.2 (benzene); 39.0 g (200 mmol) with $CsSCOC_6H_5$ (56.8 g, 210 mmol) in 350 ml DMF to give the thiobenzoate, 46.9 g (186 mmol, 93% yield), as a thick oil, which solidified on standing, mp ca. 35°C; $[\alpha]_{578}^{20}$ +33.3° (c 1.6, $CHCl_3$); ^{1}H NMR: δ 0.8-1.8 (m, 8H), 1.8-2.6 (m, 1H), 4.6 (d, 1H, J = 5 Hz), 7.3-8.2 (m, 5H) and 11.5 (s, 1H); ^{13}C NMR: δ 190.15 (s), 177.68 (s) [136.13 (s), 133.61 (d), 128.50 (d), 127.29 (d) C_6H_5] 51.55 (d), 36.56 (d), 27.32 (t), 16.51 (q) and 11.49 (q). Treatment of the thiobenzoate (44.1 g, 175 mmol) with 1N NH_3 (700 ml) gave 5f (18.1 g, 122 mmol, yield 70%) after distillation; bp 60°C/0.02 Torr, $[\alpha]_{578}^{20}$ +10.3 (c 2.4, $CHCl_3$); ^{1}H NMR: δ 0.7-2.0 (m, 9H), 1.85 (d, 1H, SH), 3.3 (dd, 1H) and 10.5 (s, 1H); ^{13}C NMR: δ 179.14 (s), 46.96 (d), 38.09 (d), 27.20 (t), 15.10 (q), 11.11 (q); exact mass calcd for $C_6H_{12}O_2S$: 148.056, found 148.058. This material was diastereomerically (^{13}C, ^{31}P NMR) and enantiomerically (^{31}P method) pure.

(2S,5R)-2-t-Butyl-5-methyl-1,3-oxathiolan-4-one (cis 6a). This compound was prepared from (optically pure) 5a and pivalaldehyde as described for the racemate,[2a] in all respects the same except for mp and rotation. Bp 65°C/0.1 Torr, mp 60-61°C, $[\alpha]_{578}^{20}$ 25.2 (c 0.25, $CHCl_3$).

(2S,5R)-5-Benzyl-2-(t-butyl)-1,3-oxathiolan-4-one (cis 6b). From 13.9 g (70 mmol) of 5b and 12.4 g (140 mmol) of pivalaldehyde 19.5 g (78%) crude 6b as a 2:1 (cis/trans) mixture was obtained. After two recrystallizations from ether/pentane (1:1) at -80°C, cis 6b (ds 97%) was obtained, mp 89.5-90.5°C; $[\alpha]_{578}^{22}$ +92° (c 0.75, $CHCl_3$); IR (KBr): 2990 (s), 1760 (s), 1195 (m), 1165 (m), 1040 (m),

1018 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.30 (s, 5H), 5.18 (d, 1H, J = 0.7 Hz), 4.28-4.18 (dd, 1H), 3.63-3.50 and 3.00-2.87 (2x dd, 2H, benzylic), and 0.99 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 173.87 (s), 137.61 (s), 128.74 (d), 128.61 (d), 127.05 (d), 88.50 (d), 48.95 (d), 38.27 (t), 34.85 (s), 24.96 (q); MS exact mass calcd for $C_{14}H_{18}O_2S$: 250.101, found 250.103; Anal: calcd for $C_{14}H_{18}O_2S$ C 67.17, H 7.25, S 12.81; found C 67.20, H 7.27, S. 12.57.

trans 6b: ^1H NMR ($CDCl_3$): δ 7.30 (s, 5H), 4.82 (s, 1H), 4.16-4.07 (dd, 1H), 3.43-3.31 and 3.15-3.05 (2x dd, 2H, benzylic), and 0.94 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 174.56 (s), 136.94 (s), 129.26 (d), 128.50 (d), 127.18 (d), 88.79 (d), 48.48 (d), 39.59 (t), 36.17 (s), and 24.6 (q).

(2S, 5R)-2-(t-Butyl)-5-(phenyl)-1,3-oxathiolan-4-one (cis 6c). From 8.45 g (50 mmol) of 5c and 8.6 g (100 mmol) of pivalaldehyde, 9.57 g (81%) of crude 6c was obtained as a 8:1 (cis/trans) mixture. Two recrystallizations from ether/pentane (1:1) at -40°C afforded cis 6c (ds >98%); mp 114-115°C; $[\alpha]^{20}_{578}$ +34.6° (c 0.5, $CHCl_3$); IR (KBr): 2980 (m), 1765 (s), 1370 (m), 1170 (m), 1160 (m), and 1018 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.39 (s, 5H), 5.34 (s, 1H), 5.10 (s, 1H), and 1.11 (s, 9H); ^{13}C NMR: δ 172.96 (s), 134.69 (s), 128.72 (d), 128.59 (d), 128.34 (d), 87.77 (d), 51.00 (d), 34.84 (s), and 24.88 (q); MS exact mass calcd for $C_{13}H_{16}O_2S$ 236.087, found 236.087; Anal. calcd for $C_{13}H_{16}O_2S$: C 66.06, H 6.83, S 13.57; found C 65.67, H 6.83, S 13.62.

trans 6c: ^1H NMR: δ 7.39 (s, 5H), 5.39 (s, 1H), 5.00 (s, 1H), 1.08 (s, 9H).

(2S, 5R)-2-(t-Butyl)-5-(isopropyl)-1,3-oxathiolan-4-one (cis 6d). From 6.7 g (50 mmol) of 5d and 8.6 g (100 mmol) of pivalaldehyde, 5.0 g (49%) 6d as a 3:1 (cis/trans) mixture was obtained after a kugelrohr distillation (bp 80°/0.1 Torr). It was not possible to separate the diastereomers; IR (neat): 2990 (m), 1790 (s), 1050 (m), and 1025 (m) cm^{-1}; ^1H NMR (major isomer): δ 5.17 (s, 1H), 4.04 (d, 4 Hz, 1H), 2.56-2.30 (m, 1H), and 1.4-0.9 (m, 15H); ^{13}C NMR (major isomer): δ 173.76 (s), 87.62 (d), 54.13 (d), 34.89 (s), 29.75 (d), 24.81 (q), 21.39 (q), and 17.50 (q); MS exact mass calcd for $C_{10}H_{18}O_2S$ 202.103, found 202.103; Anal. calcd for $C_{10}H_{18}O_2S$: C 59.37, H 8.97, S 15.85; found: C 59.22, H 8.93, S 15.65.

trans 6d: ^1H NMR: δ 5.14 (s, 1H), 3.84 (d, 4.2 Hz, 1H), 2.85-2.59 (m, 1H), and 1.4-0.9 (m, 15H).

(2S, 5R)-2-(t-Butyl)-5-(isobutyl)-1,3-oxathiolan-4-one (cis 6e). From 10.4 g (70 mmol) of 5e and 12.9 g (150 mmol) of pivalaldehyde 8.3 g (55%) 6e as a 4:1 (cis/trans) mixture was obtained after a kugelrohr distillation (120°C/0.5 Torr). Two recrystallizations from ether/pentane (1:1) at -80° gave the same cis diastereomer (6e) (ds 95%), mp 57-59°; $[\alpha]^{20}_{578}$ +75.1° (c 0.5, $CHCl_3$); IR: 2980 (s), 1770 (s), 1370 (m), 1290 (m), 1190 (m), 1045 (m), and 1010 (m) cm^{-1}; ^1H NMR: δ 5.19 (s, 1H), 3.93 (dd, 1H), 2.1-1.9 (m, 1H), 1.75-1.55 (m, 3H), 1.00 (s, 9H), and 1.0-0.9 (m, 6H); ^{13}C NMR: δ 174.94 (s), 88.27 (d), 45.24 (d), 40.95 (t), 34.55 (s), 26.98 (d), 24.71 (q), 22.74 (q), and 20.53 (q); MS exact mass calcd for $C_{11}H_{20}O_2S$ 216.118, found 216.116; Anal. calcd for $C_{11}H_{20}O_2S$: C 61.07, H 9.32, S 14.82; found: C 60.84, H 9.25, S 14.64.

trans 6e: ^1H NMR: δ 5.19 (s, 1H), 3.80 (dd, 1H), 2.1-1.9 (m, 1H), 1.75-1.55 (m, 3H), 0.98 (s, 9H), and 0.98-0.9 (m, 6H); ^{13}C NMR: δ 175.42 (s), 88.27 (d), 44.64 (d), 42.31 (t), 36.10 (s), 26.50 (d), 24.40 (q), 22.74 (q), and 20.53 (q).

(2S,5R)-2-(t-Butyl)-5-(S-2'-methylbutyl)-1,3-oxathiolan-4-one (cis 6f). From 15.7 g (106 mmol) of 5f and 17.2 g (200 mmol) of pivalaldehyde 13.4 g (61%) of 6f was obtained as a 4.5:1 (cis/trans) mixture after kugelrohr distillation (100°C/0.1 Torr). One recrystallization from ether/pentane (1:1) at -90°C gave the same cis diastereomer 6f (ds 98%), mp +5°C; $[\alpha]^{20}_{578}$ 97.8° (c 0.5, $CHCl_3$); IR: 2985 (s), 1770 (s), 1470 (m), 1290 (m), 1195 (m), 1045 (m), and 1020 (m) cm^{-1}; ^1H NMR: δ 5.18 (d, 1H, J = 0.7 Hz), 4.16 (d, 1H, J = 3.4 Hz), 2.35-2.17 (m, 1H), 1.43-1.2 (m, 2H), 1.02 (s, 9H), 0.95 (d, 3H), and 1.05-0.9 (m, 3H); ^{13}C NMR: δ 174.06 (s), 87.51 (d), 52.06 (d), 35.81 (d), 34.69 (s), 28.65 (t), 24.60 (q), 14.45 (q), and 11.23 (q); MS exact mass calcd for $C_{11}H_{20}O_2S$ 216.118, found 216.116.

trans 6f: ^{1}H NMR: δ 5.18 (d, 1H, J = 0.7 Hz), 4.00 (d, 1H, J = 3.7 Hz), 2.2 (m, 1H), 1.3 (m, 2H), 1.00 (s, 9H), 0.95 (d, 3H), and 1.05-0.90 (m, 3H); ^{13}C NMR: δ 174.84 (s), 88.59 (d), 51.70 (d), 37.62 (d), 35.94 (s), 27.77 (t), 24.17 (q), 14.07 (q), and 11.23 (q).

(2S,5S)-2-(t-Butyl)-3-(methyl)-3-(ethyl)-1,3-oxathiolan-4-one (8a). From ethyliodide (15 mmol, 2.43 g) and 1.76 g (10 mmol) of cis 6a, 8a (1.0 g, 49%) was obtained after a kugelrohr distillation as a clear oil (ds >95%), bp 90°/0.1 Torr; $[\alpha]_{578}^{20}$ -61.1° (c 1, $CHCl_3$); ^{1}H NMR: δ 5.10 (s, 1H), 1.81 (m, 2H), 1.51 (s, 3H), 1.03 (t, 3H, J = 7.3 Hz), and 0.96 (s, 9H); ^{13}C NMR: δ 177.20 (s), 86.14 (d), 55.48 (s), 34.84 (s), 33.61 (t), 24.97 (q), 24.51 (q) and 9.12 (q); MS exact mass calcd for $C_{10}H_{18}O_2S$ 202.105, found 202.106.

(2S,5S)-2-(t-Butyl)-5-(methyl)-5-(benzyl)-1,3-oxathiolan-4-one (8b). Benzylbromide (1.2 g) and 0.88 g (5 mmol) of cis 6a gave with LDA as base after a kugelrohr distillation (140°/0.1 Torr) 8b (1.12 g, 78%) (ds >95%), mp 41-42°C; $[\alpha]_{578}^{20}$ -87.9° (c 1, $CHCl_3$); ^{1}H NMR: δ 7.31 (s, 5H), 4.06 (s, 1H), 3.26 (d, 13 Hz, 1H), 2.89 (d, 13 Hz, 1H), 1.64 (s, 1H), and 0.85 (s, 1H); ^{13}C NMR: δ 177.37 (s) [135.54, 130.38, 127.99, 127.27 C_6H_5] 86.77 (d), 56.68 (s), 46.91 (t), 34.58 (s), 26.71 (q), and 24.70 (q); MS exact mass calcd for $C_{15}H_{20}O_2S$ 264.118, found 264.117; Anal. calcd for $C_{15}H_{20}O_2S$: C 68.14, H 7.62, S 12.13; found: C 68.02, H 7.62, S 12.09.

E-5-(2-Propenyl)-2-(t-butyl)-5-methyl-1,3-oxathiolan-4-one (8c) has been previously described as the racemate.[2a]

(2S,5R)-2-(t-Butyl)-5-methyl-5-phenyl-1,3-oxathiolan-4-one (8d). Methyl iodide (2 mmol, 280 mg) and cis 6c (1 mmol, 236 mg) gave with LDA as a base 0.2 g (0.8 mmol, 80% yield) of 8d as a colorless oil after a kugelrohr distillation, bp 125°C/0.01 Torr (ds >95%); $[\alpha]_{578}^{20}$ +62.1° (c 0.7, $CHCl_3$); IR: 2960 (m), 1765 (s), 1285 (m), 1190 (m), and 1045 (m) cm^{-1}; ^{1}H NMR: δ 7.75-7.30 (m, 5H), 5.35 (s, 1H), 2.06 (s, 3H), and 1.06 (s, 9H); ^{13}C NMR: δ 176.19 (s) [140.10, 128.34, 127.85, 126.92 Ph] 86.72 (d), 57.22 (s), 35.14 (s), 27.17 (q), and 24.99 (q).

(2S,5R)-2-(t-Butyl)-5-(benzyl)-5-(phenyl)-1,3-oxathiolan-4-one (8e). Benzylbromide (1.2 mmol, 2.1 g) and cis 6c (1 mmol, 236 mg) gave with LDA as a base in 90% yield 8e (0.9 mmol, 295 mg), (ds >95%), mp 119-122°C; $[\alpha]_{578}^{20}$ +18.1° (c 0.5, $CHCl_3$); ^{1}H NMR: δ 7.70-7.25 (m, 10H), 3.96 (s, 1H), 3.74 (d, 13 Hz, 1H), 3.39 (d, 13 Hz, 1H), and 0.84 (s, 9H); ^{13}C NMR: δ 175.66 (s), [140.53, 135.02, 130.88, 128.31, 127.97, 127.80, 127.45, 126.97 C_6H_5] 87.29 (d), 64.06 (s), 47.18 (t), 34.95 (s), and 24.72 (q).

(2S,5R)-2-(t-Butyl)-5-(benzyl)-5-(methyl)-1,3-oxathiolan-4-one (8f). Methyliodide (0.42 g, 3 mmol) and cis 6b (2 mmol, 472 mg) gave with LHMDS as a base after a kugelrohr distillation 8f (0.37 g, 70%), bp 120°/0.01 Torr (ds 86%); $[\alpha]_{578}^{20}$ +19.0° (c 2.7, $CHCl_2$), mp 53-56°; IR: 2960 (m), 1765 (s), 1370 (m), 1290 (m), 1090 (m), and 1050 (m) cm^{-1}; ^{1}H NMR (major isomer): δ 7.28 (s, 5H), 5.19 (s, 1H), 3.25 (d, 12 Hz, 1H), 3.16 (d, 12 Hz, 1H), 1.62 (s, 3H), and 0.92 (s, 9H); ^{13}C NMR (major isomer): δ 178.84 (s) [137.49, 131.75, 129.55, 128.51 C_6H_5] 88.44 (d), 57.79 (s), 46.45 (t), 36.27 (s), 28.08 (q), and 26.26 (q); MS exact mass calcd for $C_{15}H_{20}O_2S$ 264.118, found 264.117; Anal. calcd for $C_{15}H_{20}O_2S$: C 68.14, H 7.62, S 12.13; found: C 67.87, H 7.62, S 12.11.

(2S,5R)-2-(t-Butyl)-5-(methyl)-5-(2-methylpropyl)-1,3-oxathiolan-4-one (8g). Methyl iodide (0.7 g, 5 mmol) and cis 6e (3 mmol, 650 mg) gave with LHMDS as a base after a kugelrohr distillation 8g (0.41 g, 59%) (ds >95%), bp 90°/0.5 Torr; $[\alpha]_{578}^{20}$ -2.5° (c 0.5, $CHCl_3$); IR: 2960 (s), 1770 (s), 1370 (m), 1290 (m), 1045 (m), and 1020 (m) cm^{-1}; ^{1}H NMR: δ 5.17 (s, 1H), 1.78 (s, br, 2H), 1.54 (s, 3H), and 1.2-0.75 (m, 16H); ^{13}C NMR: δ 177.68 (s). 86.60 (d), 54.51 (s), 46.69 (t), 34.61 (s), 27.14 (d), 25.45 (q), 24.96 (q), 24.11 (q), and 22.03 (q); MS exact mass calcd for $C_{12}H_{22}O_2S$ 230.134,

found 230.135; Anal. calcd for $C_{12}H_{22}O_2S$: C 62.57, H 9.63, S 13.92; found: C 62.12, H, 9.52, S, 14.01

(2S,5S)-2-(t-Butyl)-5-(2-methylpropyl)-5-benzyl-1,3-oxathiolan-4-one (8h). Benzyl bromide (1.03 g, 6 mmol) and cis 6e (4 mmol, 864 mg) gave with LHMDS as a base after kugelrohr distillation (140°/0.01 mm) 8h (0.92 g, 76%) (ds >95%), mp 67-69°; $[\alpha]_{578}^{20}$ -44.4° (c 0.5, $CHCl_3$); ^1H NMR: δ 7.4-7.2 (m, 5H), 3.51 (s, 1H), 3.15 (s, 2H), 2.2-2.0 (m, 1H), 1.95-1.85 (m, 1H), 1.15-0.90 (m, 7H), and 0.82 (s, 9H); ^{13}C NMR: δ 177.49 (s) [135.31, 130.59, 127.99, 127.30 C_6H_5] 87.31 (d), 61.67 (s), 47.21 (t), 47.11 (t), 34.51 (s), 25.60 (d), 24.86 (q), 24.41 (q), and 22.42 (q); MS exact mass calcd for $C_{18}H_{26}O_2S$ 306.165, found 306.162; Anal. calcd for $C_{18}H_{26}O_2S$: C 70.55, H 8.55, S 10.46; found: C 70.49, H 8.56, S 10.13.

(2S,5R)-2-(t-Butyl)-5-(S-1-methylpropyl)-5-methyl-1,3-oxathiolan-4-one (8i)
Methyl iodide (1.06 g, 7.5 mmol) and cis 6f (5 mmol, 1.08 g) gave with LDA as a base 8i (0.98 g, 85%) after a kugelrohr distillation (125°/0.01 Torr) (ds 60%). The same yield and ds were obtained on use of LHMDS; IR: 2960 (m), 1765 (m), 1205 (m), and 1045 (m) cm^{-1}: ^1H NMR (major diastereomer underlined): δ 5.20/5.07 (s, 1H), 2.0-1.3 (m, 3H), 1.65/1.55 (s, 3H), 1.01/0.96 (s, 9H), and 0.93 (m, 3H); ^{13}C NMR (major isomer): 177.27 (s), 86.45 (d), 60.91 (s), 41.80 (d), 34.91 (s), 25.91 (q), 24.86 (q), 18.14 (t), and 11.66 (q); MS exact mass calcd for $C_{12}H_{22}O_2S$ 230.134, found 230.135.

(2S,5S)-2-(t-Butyl)-5-(S-1-methylpropyl)-5-benzyl-1,3-oxathiolan-4-one (8j).
A LDA solution (hexane/THF 1:1, 1N, 2.1 ml) was added at -78° to a solution of cis 6f (2 mmol, 432 mg) in 20 ml of THF. After half an hour at -80°C, benzyl bromide (2.5 mmol, 428 mg) was added and the solution was allowed to warm up to -20°C in 3 hours. Normal work up afforded a crystalline product, which was purified by kugelrohr distillation (140°/0.01 Torr) to give pure 8j (580 mg, 90% yield) (ds >95%), mp 96.5-97.0°; $[\alpha]_{578}^{20}$ -12.5° (c 0.6, $CHCl_3$): IR: 2960 (m), 17.55 (s), 1370 (m), 1290 (m), 1165 (m), and 1045 (m); ^1H NMR: δ 7.4-7.2 (m, 5H), 3.51 (s, 1H), 3.16 (s, 2H), 2.2-2.0 (m, 1H), 1.95-1.75 (m, 1H), 1.2-0.9 (m, 7H), and 0.79 (s, 9H); ^{13}C NMR: δ 177.10 (s) [135.84, 130.74, 127.95, 127.20] 87.57 (d), 68.51 (s), 45.15 (t), 42.82 (d), 34.81 (s), 25.15 (t), 24.85 (s), 15.42 (q), and 11.87 (q); MS exact mass calcd for $C_{18}H_{26}O_2S$ 306.165, found 306.165; Anal. calcd for $C_{18}H_{26}O_2S$: C 70.55, H 8.55, S 10.46; found: C 70.42, H 8.50, S 10.43.

(2S,5S)-2-(t-Butyl)-5-(1-hydroxy-1-methylethyl)-5-methyl-1,3-oxathiolan-4-one (10a). Acetone (4 mmol, 0.32 g) and cis 6a (2 mmol, 0.348 g) gave after flash chromatography (ether/pentane 1:15) 0.188 g (40%) of 10a (ds >95%); $[\alpha]_{578}^{20}$ -5.5° (c 0.5, $CHCl_3$); ^1H NMR: δ 5.52 (s, 1H), 3.40 (s, 1H), 1.75 (s, 3H), 1.31 (s, 3H), 1.25 (s, 1H), and 1.00 (s, 9H); ^{13}C NMR: δ 178.03 (s), 86.56 (d), 73.95 (s), 62.08 (s), 34.90 (s), 26.84 (q), 24.90 (q), and 22.01 (q).

(2S,5S)-2-(t-Butyl)-5-methyl-5-(1-hydroxy-1'-phenylmethyl)-1,3-oxathiolan-4-one (10b). Benzaldehyde (222 mg, 2.1 mmol) and cis 6a (2 mmol, 348 mg) gave after chromatography (silica gel 60, pentane/ether 15:1) 275 mg (49%) of 10b as a 55:45 mixture of diastereomers (at C-1') (ds 10%); ^1H NMR (major diastereomer underlined): δ 7.3 (s, 5H), 5.12/4.02 (s, 1H), 5.00/4.90 (s, 1H), 3.0 (br, 1H), 1.66 (s, 3H), and 1.00/0.97 (s, 9H).

(2S,5S)-2-(t-Butyl)-5-(1'-hydroxy--1-ethyl)-5-methyl-1,3-oxathiolan-4-one (10c). Acetaldehyde (2.5 mmol, 113 mg) and cis 6a (2 mmol, 348 mg) gave with LDA as a base a mixture of products. After chromatography (silica gel 60, pentane/ether 15:1) 10c was obtained as a 2:1 mixture of diastereomers at C-1' (ds 33%) (yield 45%); ^1H NMR (major diastereomer underlined): δ 5.21/5.13 (s, 1H), 4.05 (m, 1H), 2.30/3.30 (br, 1H), 1.62/1.66 (s, 3H), 1.27/1.22 (d, 10 Hz, 3H), and 1.00 (s, 9H).

(2S,5S)-2-(t-Butyl)-5-(1-hydroxy-1-methyl-2-propenyl)-5-methyl-1,3-oxathiolan-4-one (11). Methylvinylketone (8 mmol, 0.56 g) was added at -80° to a solution of the enolate of cis 6a (6 mmol, 1.06 g) in 40 ml of THF (see for 8a). The mixture was stirred at -80°C for 1 hour and then was worked up in the usual manner. Flash chromatography (ether/pentane 1:15) afforded the 1,2-adduct 11 (1.03 g, 70%) as a mixture of two diastereomers at C-1' (ds 20%). No 1,4-adducts were observed; ^{1}H NMR (major diastereomer underlined): δ 6.5-5.0 (m, 3H), 5.13/5.10 (s, 1H), 2.85/2.75 (s, 1H), 1.63/1.58 (s, 3H), 1.47/1.42 (s, 3H), and 1.0 (s, 9H).

(2S,5S)-2-(t-Butyl)-5-(3-butane-3-one)-5-methyl-1,3-oxathiolan-4-one (12). A cold solution of the enolate of cis 6a (5 mmol) in 40 ml of THF was warmed to +15°C. The solution remained clear and colorless. When methylvinylketone (7 mmol, 0.49 g) was added, the solution immediately turned yellow. The solution was allowed to stir for 10 min and then was worked up normally. Flash chromatography (pentane/ether 15:1) gave the crude 1,4-adduct 12 (ds >95%) in 85% yield; bp 130°/0.01 Torr; ^{1}H NMR: δ 5.13 (s, 1H), 2.8-2.5 (m, 2H), 2.17 (s, 3H), 2.3-2.0 (m, 2H), 1.53 (s, 3H), and 1.0 (s, 9H). By means of kugelrohr distillation a small nonidentified impurity, bp 90°/0.1 Torr, was removed. The 1,2-addition product could not be detected.

Methyl-(S)-2-mercapto-2-methyl-butanoate (9a). Transacetalization of 8a (CH_3OH sat. with HCl, reflux, 2 days) gave 9a after distillation, bp 110°/1 Torr (70% yield); ^{1}H NMR: δ 3.70 (s, 3H), 2.2-1.4 (m, 2H), 1.40 (s, 3H), and 0.90 (t, 3H); ee (^{31}P method) >95%.

(S)-2-Mercapto-2-methyl-3-phenyl-propanoic acid (9b). Basic hydrolysis of 8b (CH_3OH/LiOH, reflux 2 days) gave 9b after a kugelrohr distillation (65% yield), bp 120°/0.01 Torr; $[\alpha]^{20}_{578}$ +31.9° (c 1, $CHCl_3$); IR: 1700 cm^{-1} (C=O); ^{1}H NMR: δ 7.25 (s, 5H), 3.33 (d, 1H, 13 Hz), 3.00 (d, 1H, 13Hz), 3.41 (s, 1H), 1.34 (s, 3H), and 11.2 (s, br, 1H); ^{13}C NMR: δ 180.59 (s) [135.98, 130.31, 128.17, 127.14 C_6H_5] 49.14 (s), 47.50 (t), 24.41 (q). The methyl ester prepared from this sample showed ee >95% (^{31}P method).

Methyl (R)-2-mercapto-2-methyl-2-phenylacetate (9c). Transacetalization of 8d (CH_3OH/HCl, reflux 2 days) afforded 9c after a kugelrohr distillation, bp 110°/0.1 Torr; ^{1}H NMR: δ 7.6-7.3 (m, 5H), 3.73 (s, 3H), 2.72 (s, 1H), and 1.87 (s, 3H); ee (^{31}P method) 91%.

(R)-2-Mercapto-2-methyl-3-phenylpropanoic acid (9d). Acid hydrolysis of 8f (CH_3OH/6N HCl 2:1, reflux 4 days) gave 9d (60%). Its physical properties were identical to its enantiomer 9b except for the rotation and ee, $[\alpha]^{20}_{578}$ -24.6° (c 1, $CHCl_3$), ee (^{31}P) 75%.

(R)-2-Mercapto-2-benzyl-4-methylpentanoic acid (9e). Transacetalization of 8g (CH_3OH/HCl, reflux 1 week) gave 9e; ^{1}H NMR: δ 7.23 (s 5H), 3.67 (s, 3H), 3.32 (d, 1H, 13 Hz), 2.94 (d, 1H, 13Hz), 2.05 (s, 1H), 1.90 (m, 1H), 0.95 (m, 6H); ee (^{31}P method) 78%.

(R)-2-Mercapto-2-benzyl-(S)-3-methylpentanoic acid (9f). Basic hydrolysis (LiOH/CH_3OH, reflux 6 days) of 8j gave, after acidification, crude 9f, which was purified by short column chromatography (silica gel 60, $CHCl_3$, Rf ~ 0.15) to give a colorless oil; $[\alpha]^{20}_{578}$ -52.6° (c 1.4, $CHCl_3$); ^{1}H NMR: δ 10.5 (s, 1H), 7.30 (s, 5H), 3.32 (d, J = 13 Hz, 1H), 2.96 (d, J = 13 Hz, 1H), and 2.25-0.8 (m, 10H); ^{13}C NMR: δ 178.77 (s) [136.15, 130.78, 128.26, 127.68 C_6H_5] 44.70 (s), 44.56 (d), 43.64 (t), 24.44 (t), 14.99 (q), and 12.38 (q). This material was diastereomerically (^{13}C, ^{31}P) and enantiomerically (^{31}P method) pure.

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15. We also prepared the acetal from (racemic) 5a and chloral,[14a] which gave a 2:1 (cis/trans) mixture. This was alkylated with benzylbromide to give a mixture of products. Although the desired quaternary thiol was present, as determined by ^{1}H NMR, by-product formation (probably due to self alkylation of the trichloromethyl group) was substantial.
16. Of course, the ortho and meta hydrogens in 8e are diastereotopic. But this, in our experience, normally does not give rise to such a broad absorption.
17. Sometimes some starting material was found. Reactions with acetophenone and benzophenone were very slow. After normal reaction times, mainly starting material was recovered. These reactions were not investigated further.
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19. For racemic 9b, the separation between the d,l pair and two meso isomers are Δδ 16 and 39 Hz; for racemic 9a and 9b, which can both be taken as a reference, the separations are Δδ 242 and 65 Hz and Δδ 182 and 82 Hz, respectively.
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