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Synthesis of Chiral Hydroxythiolanes as Potential Catalysts for Asymmetric Organozinc Additions to Carbonyl Compounds

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ABSTRACT: *Optically active 3-hydroxythiolane was stereospecifically synthesized from L-aspartic acid and oxidized to give both diastereomeric S-oxides, which were chromatographically separated and their configuration was determined. Starting from natural (+)-(R,R)-tartaric acid, C_2-symmetric trans-(R,R)-3,4-dihydroxythiolane was stereospecifically synthesized for the first time. Some of its monofunctionalized derivatives as well as its S-oxide were also obtained and characterized. meso-cis-3,4-Dihydroxythiolane was obtained in a similar way from meso-tartaric acid and subjected to desymmetrization either by a lipase-promoted acetylation or hydrolysis of the corresponding O,O′-diacetyl derivative, to give a chiral monoacetate with ee up to 36%. After its oxidation two diastereomeric sulfoxides were obtained which were separated by chromatography. The crystalline one was subjected to X-ray analysis and its absolute configuration was determined as 1S, 3S, 4R. All the optically active products were checked as potential catalysts for asymmetric addition of diethylzinc to benzaldehyde. However, they proved to have a very low catalytic activity: yields of the products were in the range 10–90% but ee only up to 10%. A conclusion was drawn that in this type of reaction neither is the hydroxy sulfide (sulfoxide) moiety capable of properly binding diethylzinc, nor does the sulfinyl group exert its normal stereoinduction.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:93–103, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20076

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INTRODUCTION

Although 19 years have already passed since the initial report on the asymmetric addition of diethylzinc

to benzaldehyde in the presence of leucinol [1], a search for new chiral catalysts for this type of reaction still continues. Over the two decades a large variety of such catalysts has been developed, as may be seen from several overviews which came out in this period, the last most comprehensive being the one written by Pu and Yu in 2001 [2]. An inspection of the types of compounds that exhibit such a catalytic activity clearly indicates that the most efficient are chiral aminoalcohols. In a few cases the hydroxy group has been successfully replaced by a thiol moiety, in some other—only the hydroxy groups (polyols) or amino groups (polyamines) were present in the catalyst molecule. It is noteworthy that practically in all cases, it is one or more stereogenic carbon atoms that served as a source of chirality or the catalyst molecule was created on the basis of an axially chiral substrate. Very few catalysts were used which possessed a stereogenic centre located on a heteroatom such as P or S. There are practically only two examples of sulfur-based catalysts containing S-chiral moieties: hydroxyalkylsulfoximines, prepared by Bolm et al. [3a] and β-hydroxyalkylsulfoxides, obtained by Carreno et al. [3b]; both types of compounds were used as catalysts for the enantioselective diethylzinc additions to carbonyls with moderate success. The latter type of compound was also applied as a chiral component of the catalysts for the enantioselective Diels-Alder cycloadditions [3c]. The limited number of chiral sulfoxides used as catalysts is particularly surprising as they are known to exert high asymmetric induction [4] and to easily form complexes with organometallic reagents. Having this in mind, we have decided to synthesize and to examine various types of optically active hydroxy sulfoxides and their derivatives for their applicability as catalysts for the above reaction. We have focused our attention particularly on the derivatives of hydroxythiolanes that contain both the hydroxyl function and the sulfide or sulfoxide moiety within the ring. Such a constitution may be expected to secure an efficient hindering of one side of the catalyst and thus promote a highly enantioselective transformation.

RESULTS AND DISCUSSION

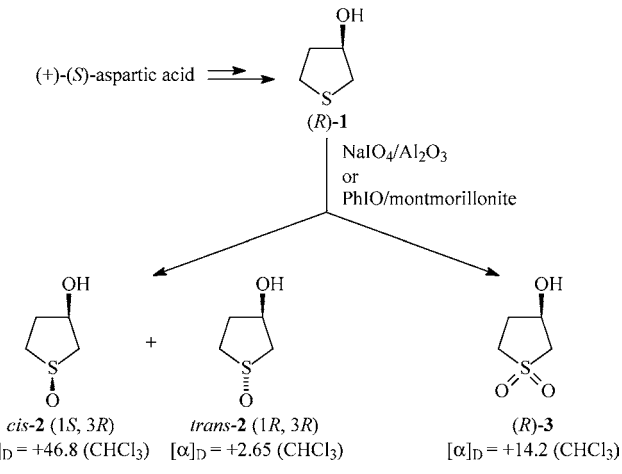
Synthesis of 3-Hydroxythiolane S-Oxide

The synthesis of 3-hydroxythiolane **1** was performed according to the procedure described by Volkmann et al. [5]. Its oxidation, using a $NaIO_4/Al_2O_3$ system [6] or iodosobenzene in the presence of montmorillonite [7], gave a diastereomeric mixture of *cis* and *trans* sulfoxides **2**, which were separated by column chromatography. Their absolute configuration was ascribed on the basis of the publication by Quallich and Lackey [8], and the particular diastereomers were fully characterized. Additionally, the corresponding sulfone **3** was also isolated (Scheme 1).

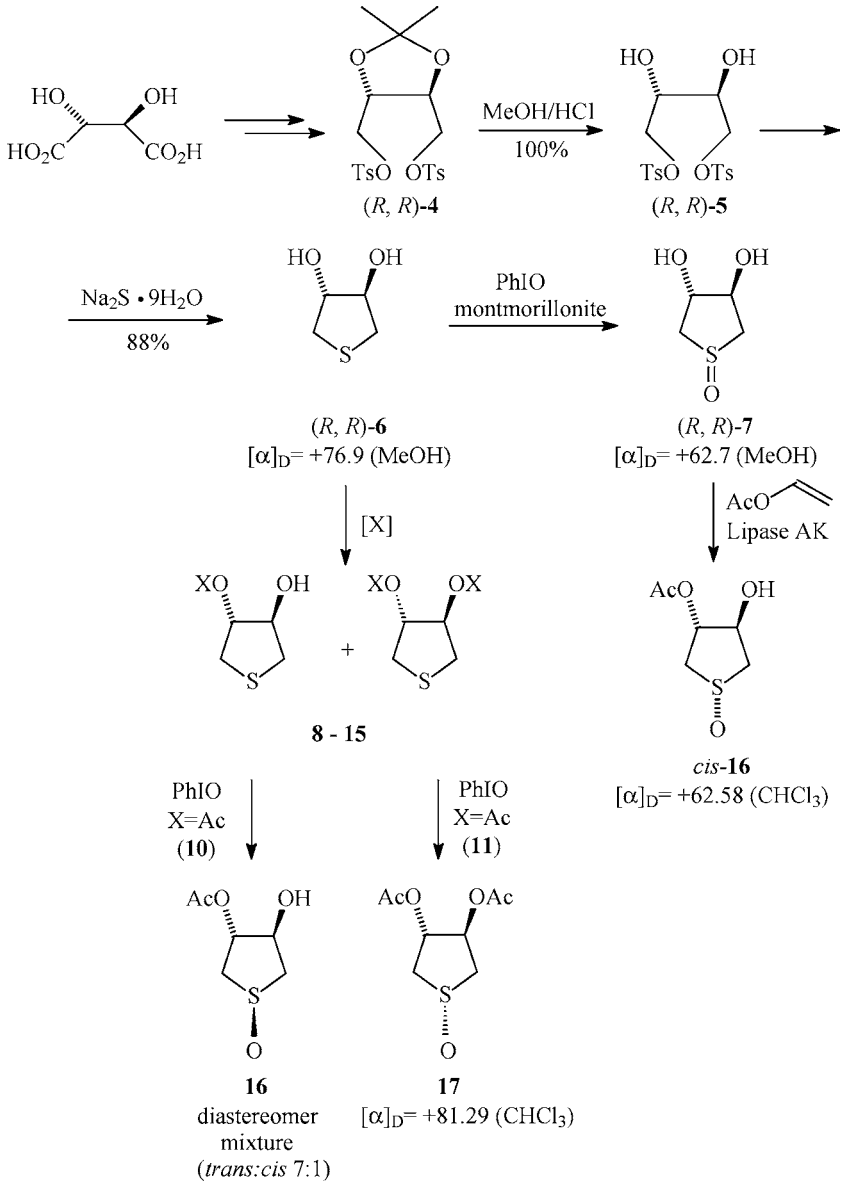
The compounds **1** and **2** were expected to be good catalysts for the reaction under discussion, by analogy with structurally similar 3-hydroxypyrrolidine [9] which was found to lead to the addition products with ee >90%.

Synthesis of trans-(R,R)-3,4-Dihydroxythiolane and its Derivatives

The synthesis of *trans*-(*R*,*R*)-3,4-dihydroxythiolane **6** was accomplished as shown in Scheme 2. Using simple and commonly known procedures, natural (+)-(*R*,*R*)-tartaric acid was transformed into properly protected L-threitol **4**. An attempt to perform its direct reaction with sodium sulfide proved unsuccessful due to the volatility of the expected product. Therefore, the acetonide protecting group was removed first to give butanetetraol 1,4-ditosylate **5**, which was ultimately transformed into the desired product **6**. This product, having a C_2 symmetry, seemed also very promising, as a variety of different types of C_2-symmetric compounds were extensively studied and proved to be efficient catalysts, e.g. *trans*-1,2-bis(trifluoromethanesulfonamido)cyclohexane [10]. Oxidation of **6** led to the formation of one sulfoxide **7** in which the sulfinyl moiety is not a stereogenic center. Moreover, the sulfoxide **7** is no more a C_2-symmetric compound, since the sulfinyl oxygen atom is in a *trans* position to one of the hydroxy groups and *cis* to the other one. As we expected that the two different relations between the hydroxy and sulfinyl groups may result in exerting an opposite stereochemical effect,



SCHEME 1



[X]	X	Monofunctionalized			Difunctionalized		
			Yield (%)	$[\alpha]_D$ ($CHCl_3$)		Yield (%)	$[\alpha]_D$ ($CHCl_3$
$BuLi/Me_3SiCl$	$SiMe_3$	**8**	28	+46.4	**9**	37	+58.6
$Ac_2O/Yb(OTf)_3$	Ac	**10**	54	+72.9	**11**	18	+112.0
$NaH/PhCH_2Br$	Bn	**12**	15	+70.7	**13**	14	+82.6
$TsCl/Et_3N$	Ts	**14**	46	+38.6	**15**	36	+13.0

SCHEME 2

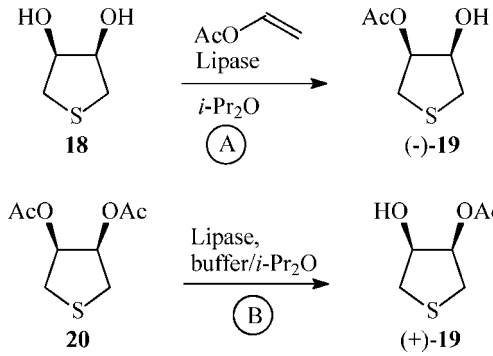
we decided to selectively functionalize the hydroxy groups. Two approaches were used: functionalization of one of the equal hydroxy groups in **6** prior to sulfoxidation, and functionalization of the nonequivalent hydroxy groups in the sulfoxide **7**. The first approach comprised monosilylation, monoacetylation, monobenzylation, and monotosylation of **6**. For obvious reasons, the desired products **8, 10, 12**, and **14**, respectively were accompanied by the products of a double functionalization, i.e. **9, 11, 13**, and **15**, respectively. However, of the monofunctionalized products only **10** was subjected to oxidation to give

the sulfoxide **16** as an inseparable diastereomer mixture (d.r. 7:1 with the *trans* prevailing). Nevertheless, all the remaining monofunctionalized products were also checked as potential catalysts (vide infra). The second approach consisted of several attempts at the enzymatic diastereoselective formation of **16**, via either a lipase-catalyzed acetylation of **7** or an enzyme-catalyzed hydrolysis of the *O*,*O*′-diacetoxy sulfoxide **17**, of which only one was successful, namely the acetylation of the sulfoxide **7** in the presence of lipase AK (AMANO). The reaction proved to be highly diastereoselective and resulted in the formation of *cis*-**16** (thus the minor diastereomer formed in the oxidation of **10**) in 65% yield, accompanied by small amounts of the diacetyl derivative **17**.

Synthesis of meso-cis-3,4-Dihydroxythiolane and its Enzymatic Desymmetrization

The synthesis of the derivatives of *cis*-3,4-dihydroxythiolane **18** was undertaken to complement the investigations of the stereochemical influence of variously constructed dihydroxythiolane molecules on the possible catalyst activity. It was performed in an analogous way as the preparation of **6**, but using *meso*-tartaric acid as a precursor (Scheme 3). The compound **18** was earlier described in the literature, but its preparation involved other substrates [11].

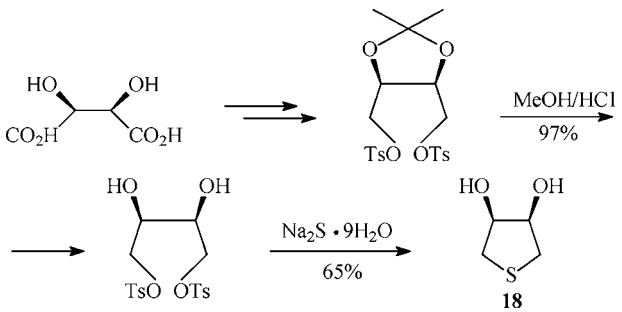
To transform the *meso* compound **18** into a chiral derivative, its desymmetrization was carried out to produce the monoacetate **19** in either of two possible ways: an enzymatic acetylation of **18** (A) and enzymatic hydrolysis of the diacetate **20** (B) (Scheme 4). In both cases, the enzymatic reactions were performed in an organic solvent, diisopropyl ether, which for the hydrolysis was saturated with a phosphate buffer (pH 7.2). It should be noted that the application of the two reverse procedures enabled us to obtain each enantiomerically enriched form of **19** (for the determination of ee and of the absolute configuration see below). This is due to a



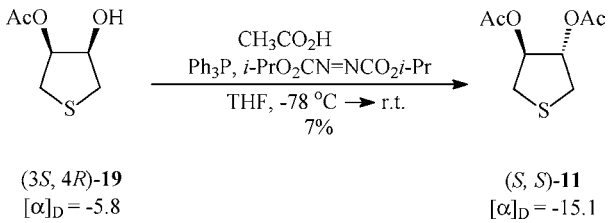
Lipase	Method	Yield (%)	$[\alpha]_D$ ($CHCl_3$)	ee (%) (at least)	Abs. conf.
AMANO PS	A	81	−13.7	36	3*S*, 4*R*
AMANO AK	A	34	−5.8	13.5	3*S*, 4*R*
AMANO PS	B	28	+2.85	7	3*R*, 4*S*

SCHEME 4

common feature of enzymes that exhibit the same sense of enantioselectivity toward substrates, irrespective of direction of the reversible reaction they catalyze (e.g. ester formation versus ester hydrolysis). Another point which should be stressed is that **19** turned out to be configurationally stable in contrast to its carba analogue, namely *cis*-1-acetoxy-2-hydroxycyclopentane which was found to undergo fast racemization due to a 1,2-acetyl shift [12]. However, certain further experiments have cast doubt on this stability. Thus, several attempts at the determination of the absolute configuration and enantiomeric excess of monoacetates **19** have been unsuccessful due to the loss of optical activity of the products obtained. For example, the reaction of (−)-**19** with tosyl chloride in the presence of triethylamine led to *cis* 2-tosyloxy-3-acetoxythiolane which showed practically no optical rotation. A similar situation was observed when silylation of (−)-**19** was undertaken. The only transformation that was partially successful and allowed chemical correlation was the Mitsunobu reaction [13] of (−)-**19** with acetic acid (Scheme 5).



SCHEME 3



SCHEME 5

As a result, *trans*-diacetoxythiolane (−)-**11** was obtained, whose absolute configuration and specific rotation is known from Scheme 2. As the Mitsunobu reaction proceeds with inversion of configuration at the hydroxyl carbon atom and the absolute configuration of (−)-**11** obtained is (*S*, *S*), the absolute configuration of (−)-**19** must be (3*S*, 4*R*). The optical rotation of (−)-**11** obtained $[\alpha]_D = -15.1$ indicates that its enantiomeric excess is 13.5%. This means that the enantiomeric excess of the starting (−)-**19**, having $[\alpha]_D = -5.8$, must be at least 13.5%. It can of course be higher, as the racemization of (−)-**19** during the reaction cannot be excluded.

Another attempt to determine the absolute configuration of **19** consisted of its oxidation in the hope of obtaining a crystalline sulfoxide for an X-ray analysis. As a result, two diastereomeric sulfoxides were formed in a comparable proportion that could be separated by a careful slow column chromatography (Scheme 6).

Gratifyingly, one of the diastereomers turned out to be crystalline and after an additional crystallization from benzene gave a sample suitable for an X-ray analysis. Although its specific rotation was very low, it proved to be a pure enantiomer, as could be deduced from the value of the Flack coefficient ($\chi = 0.01(3)$). Its absolute configuration was (1*S*, 3*S*, 4*R*) (vide infra), thus the same at the C_3 and C_4 of the thiolane ring as determined via the Mitsunobu reaction.

X-ray Analysis of **21a***—Determination of its Absolute Configuration*

As can be seen from the molecular structure of **21a** that is shown in Fig. 1, the absolute configurations at the particular stereogenic centers of the molecule are 1*S*, 3*S*, and 4*R*. This, in other words, means that the sulfinyl oxygen atom is situated in a *trans* position to both remaining oxygen atoms, which in turn are obviously in a *cis* relation. The five-membered thiolane ring adopts the conformation of an open envelope with C3 (connected with the acetoxy moiety) as an opening atom. The envelope is, however, strongly distorted (see the data in the Experimental section). The observed difference in the length of both C—S bonds (0.03 Å, 10 δ) may be explained by different conformations at C3 (pseudoequatorial) and C4 (pseudoaxial); the same can account for the difference in the lengths of C2—C3 and C4—C5 bonds (0.028 Å).

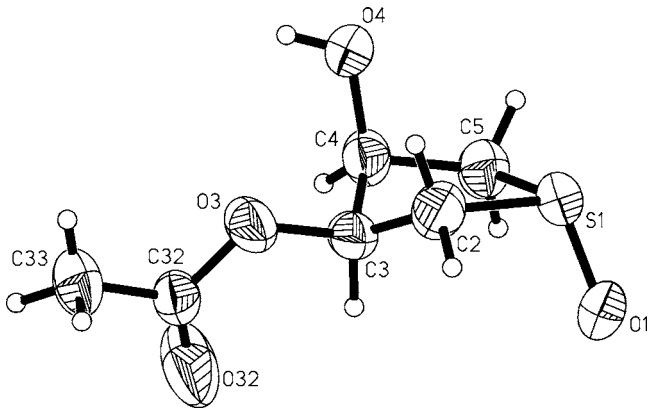
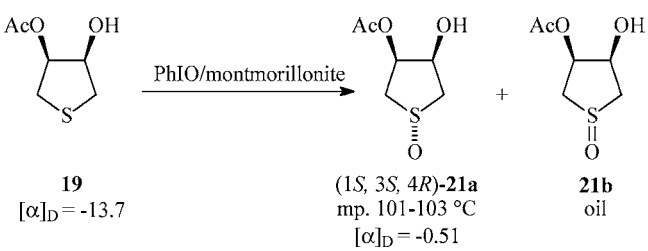


FIGURE 1 Thermal ellipsoidal view with atom numbering in the **21a** molecule. Ellipsoids are shown with 50% probability.

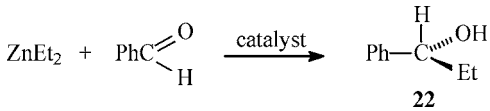
Attempts at the Application of the Hydroxythiolane Derivatives as Catalysts

All the chiral products described in previous sections were checked for their catalytic activity in the asymmetric addition of diethylzinc to benzaldehyde that was chosen as a reference reaction (Scheme 7). The results are collected in Table 1.

Unfortunately, all the hydroxythiolane derivatives proved to be inefficient as catalyst for the above reaction. Not only were the yields generally low (with some exceptions), but the ee of the alcohol **22** never exceeded 10% in spite of applying a variety of solvents, additives, and conditions. Some side-products were always formed, among them was benzyl alcohol which is known to arise from benzaldehyde as a result of its reduction by diethylzinc [14]. Practically no difference was observed in the enantiomeric excess of **22** when a sulfoxide was used instead of the corresponding sulfide or sulfone (entries 1–4 and 9, 10 versus entries 5–8, 11–13 versus 14–17, 23 versus 24



SCHEME 6



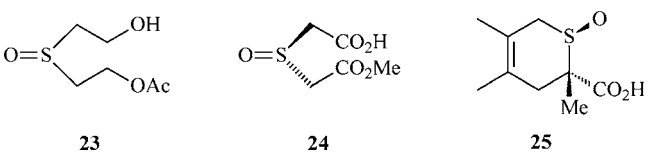
SCHEME 7

TABLE 1 Asymmetric Diethylzinc Additions to Benzaldehyde Yielding **22**

Entry	*Catalyst*	*Solvent*	*Additives*	*Yield (%)*	$[\alpha]_D$ *($CHCl_3$)*	*ee (%)*
1	**1**	Benzene	–	60	+2.8	7
2	**1**	Cyclohexane	–	25	+4.4	10
3	**1**	Toluene	–	30	+4.1	9
4	**1**	Toluene	BuLi	41	−0.9	<5
5	*cis*-**2**	Toluene	BuLi	30	+2.6	7
6	*cis*-**2**	Benzene	–	60	+7	16
7	*trans*-**2**	Benzene	–	60	−0.5	<5
8	*trans*-**2**	Cyclohexane	–	50	−1.2	<5
9	**3**	Cyclohexane	–	20	−0.7	<5
10	**3**	Benzene	–	25	+1.0	<5
11	**6**	Benzene		30	+0.9	<5
12	**6**	Toluene	BuLi	30	0	0
13	**6**	Toluene	$Ti(OiPr)_4$	50	−0.7	<5
14	**7**	Benzene	–	50	+0.5	<5
15	**7**	Toluene	BuLi	50	+0.8	<5
16	**7**	Toluene	$Ti(OiPr)_4$	60	+2.3	6
17	**7** equimolar	Toluene	$Ti(OiPr)_4$	90	+3.3	8
18	**10**	Benzene	–	20	+4.5	10
19	**12**	Benzene	–	15	+3.5	8
20	**14**	Benzene	–	15	−1.0	<5
21	**16** (diast.mixt.)	Benzene	–	10	−1.2	<5
22	*cis*-**16**	Benzene	–	36	−2.36	6
23	**19**	Benzene	–	10	−1.0	<5
24	*cis*-**21**	Benzene	–	15	−0.7	<5
25	*trans*-**21**	Benzene	–	15	−0.4	<5
26	**23**	Benzene	–	10	+2.2	<5
27	**24**	Benzene	–	20	+6.2	14
28	**25**	Benzene	–	67	−0.3	<5
29	**26**	Benzene	–	60	−16	36
30	**27**	Benzene	–	50	−14	32
31	**28**	Benzene	–	13	−3.3	8

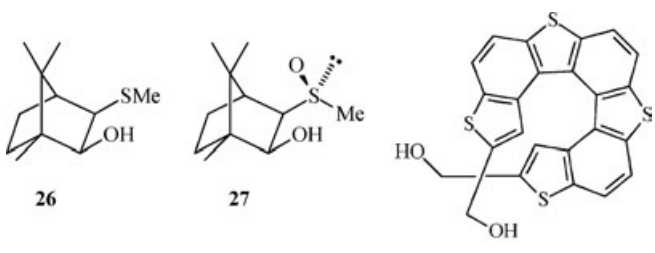
and 25) that indicates a complete lack of the asymmetric induction of the sulfinyl group. Location of both potential diethylzinc-binding sites (S or SO and OH) in a ring, even in a *cis* relation (entries 5, 6, and 24), proved to be also an insufficient factor to induce an enantiofacial differentiation of the reagent. Moreover, the use of an open-chain hydroxy sulfoxide [15] **23** (entry 26) gave a comparable result (see Scheme 8). Application of a chiral carboxy sulfoxide [15] **24** (entry 27) slightly improved the ee of **22**; however, the yield was very low. The cyclic carboxy sulfoxide [16] **25**, although sterically more congested, gave a completely disappointing result (entry 28). Finally, the camphor-derived highly hindered sulfide **26** and sulfoxide **27** (Scheme 9), synthesized according to the method described by Ridley et al. [17], proved to be the best catalysts from among all so far tested, although still far from expectations (entries 29 and 30). Moreover, as there was no difference in the enantioselection between sulfide **26** and sulfoxide **27**, the influence of the SO chiral group seems negligible.

The last compound **28**, synthesized by Tanaka et al. [18], having a helical chirality ($[\alpha]_D = -1973$,



23 **24** **25**

SCHEME 8



26 **27** **28**

SCHEME 9

$c = 0.055$, $CHCl_3$) also proved to be inefficient as a catalyst (entry 31). Because of the generally disappointing results obtained, no attempts were made to change the aldehyde applied or replace diethylzinc with other organozinc derivatives.

On the basis of the negative results presented, a conclusion can be drawn that the hydroxy sulfide or hydroxy sulfoxide moiety is incapable of properly binding diethylzinc, most probably due to the insufficient basicity of the sulfur and sulfinyl oxygen centers. The diethylzinc-catalyst complex is either not formed or its reactivity is very low, which can be seen from the low yields of the desired alcohol **22** and the formation of by-products resulting from concurrent reactions. Obviously, in such a case even introducing a steric hindrance could not substantially improve the yield and stereoselectivity. This may also account for the fact that the chiral sulfinyl group does not exert any stereoinduction unlike in many other cases known from the literature.

EXPERIMENTAL

NMR spectra were recorded on Bruker instruments at 200 MHz for ^{1}H and 81 MHz for ^{31}P, with CD_3OD or $CDCl_3$ as solvents. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Column chromatography was carried out using Merck 60 silica gel. TLC was performed on Merck 60 F_{254} silica gel plates. The enzymes were purchased from AMANO or FLUKA.

Synthesis of (R)-3-Hydroxythiolane-1-oxide **2**

To a solution of **1** [5] (0.5 g, 4.8 mmol) in acetonitrile (20 mL) was added PhIO (1.058 g, 4.8 mmol) and montmorillonite K 10 (1.058 g). The mixture was stirred at room temperature until the substrate was completely consumed, as was detected by TLC ($CHCl_3$–MeOH 15:1). The precipitate was filtered off and washed with substantial amounts of a 1:1 mixture of $CHCl_3$ and MeOH. The filtrate was evaporated to give a crude reaction mixture (1.5 g) The latter was purified by column chromatography using hexane–*i*-PrOH (1:3) as eluent to afford:

cis- sulfoxide **2**: (0.226 g, 40%), $[\alpha]_D = +46.8$ ($c = 2.26$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.10$–2.35 (m, 2H), 2.55–3.50 (m, 4H), 3.50 (s, 1H), 4.77 (m, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 35.28$, 52.77, 59.01, 75.47. MS (CI): m/z 121 (M+1);

trans- sulfoxide **2**: (0.226 g, 40%), $[\alpha]_D = +2.65$ ($c = 2.26$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.15$–3.50 (m, 2H), 4.86 (m, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 34.31$, 50.77, 64.28, 72.21. MS (CI): m/z 121 (M+1); and sulfone **3**: (0.070 g, 11%), $[\alpha]_D = +14.2$ ($c = 1.18$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.25$–3.50 (m, 2H), 3.85 (s, 1H), 3.05–3.45 (m, 4H), 4.70–4.80 (m, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 31.77$, 49.55, 59.35, 67.95. MS (CI): m/z 137 (M+1).

Similar results were obtained when the $NaIO_4$/Al_2O_3 was used as an oxidizing agent.

Synthesis of 1,4-Ditosyl-2,3-O-isopropylidene-L-threitol **4**

A solution of 2,3-*O*-isopropylidene-L-threitol, obtained from L-tartaric acid [19], (1.9 g, 0.012 mol) in pyridine (14 mL) was cooled to -10°C and tosyl chloride (7.145 g, 0.037 mol) was added. The mixture was stirred overnight at room temperature. Water (80 mL) was added and the mixture was left for 2 h in a refrigerator. The precipitate was filtered, washed with water and EtOH, to give, after drying, **4** (4.409 g, 80%), $[\alpha]_D = -12.75$ ($c = 1.09$, $CHCl_3$).

^{1}H NMR ($CDCl_3$): $\delta = 1.29$ (s, 6H), 2.46 (s, 6H), 4.01 (m, 2H), 4.10 (m, 4H), 7.33–7.81 (m, 8H).

Synthesis of 1,4-Ditosyl-L-threitol **5**

To a solution of **4** (0.3 g, 0.641 mmol) in methanol (5 mL) was added 0.5 N hydrochloric acid (a few drops) and the resulting mixture was refluxed for 5 h (TLC control: hexane–ethyl acetate 2:1). The solvents were removed under vacuum, the residue was dissolved in $CHCl_3$ and dried over $MgSO_4$. After filtration and evaporation **5** was obtained (0.275 g, 100%), $[\alpha]_D = +1.05$ ($c = 1.33$, $CHCl_3$).

^{1}H NMR ($CDCl_3$): $\delta = 2.45$ (s, 6H), 3.25–3.97 (m, 2H), 4.05–4.13 (m, 4H), 7.33–7.83 (m, 8H). MS (FAB): m/z 431 (M+1).

Synthesis of (R,R)-3,4-Dihydroxythiolane **6**

A mixture of **5** (0.267 g, 0.624 mmol) and $Na_2S \cdot 9H_2O$ (0.374 g, 1.559 mmol) in EtOH (5 mL) was refluxed for 5 h (TLC control: ethyl acetate–hexane 2:1). After filtration through Celite and evaporation the residue was dissolved in $CHCl_3$. The precipitate was filtered off and washed with a large amount of $CHCl_3$. The solvent was removed under vacuum and the residue was purified by column chromatography, using $CHCl_3$ to $CHCl_3$–MeOH 10:1 (in gradient) as solvent to give **6** (65 mg, 88%), $[\alpha]_D = +76.9$ ($c = 1.22$, MeOH).

^{1}H NMR (CD_3OD): $\delta = 2.63$–3.13 (m, 4H), 4.17–4.23 (m, 2H). ^{13}C NMR (CD_3OD): $\delta = 36.19$, 79.08. MS (CI): m/z 121 (M+1). HRMS calcd. for $C_4H_9SO_2$ (M+1) 121.0322; found 121.0323.

Synthesis of (R,R)-3,4-Dihydroxythiolane-1-oxide **7**

To a solution of **6** (0.5 g, 4.167 mmol) in acetonitrile (40 mL) was added PhIO (0.917 g, 4.167 mmol) and montmorillonite K 10 (0.917 g). The mixture was stirred at room temperature until the substrate was completely consumed (TLC ethyl acetate–methanol 9:1). After filtration and evaporation, the crude reaction mixture was purified by column chromatography using AcOEt–MeOH 30:1 to AcOEt–MeOH 9:1 as eluent to give **7** (0.331 g, 58%), $[\alpha]_D = +62.7$ ($c = 1.11$, MeOH).

^{1}H NMR (CD_3OD): $\delta = 2.77$–3.66 (m, 4H), 4.42–4.59 (m, 2H). ^{13}C NMR (CD_3OD): $\delta = 58.35$, 61.12, 78.46. MS (CI): m/z 137 (M+1).

Synthesis of (R)-3-(Trimethylsilyl)-(R)-4-hydroxythiolane **8** *and (R,R)-3,4-Di(trimethylsilyl)thiolane* **9**

To a solution of **6** (0.116 g, 0.967 mmol) in THF (5 mL), a 2.5 M solution BuLi in hexane (0.45 mL, 1.125 mmol) and chlorotrimethylsilane (0.147 mL, 0.126 g, 1.160 mmol) were added at room temperature and the mixture was stirred overnight (TLC control: ethyl acetate–hexane 2:1). After the substrate was completely consumed the solution was evaporated. The residue was purified by column chromatography using AcOEt–hexane 1:20 to AcOEt–hexane 2:1 as solvent to give:

8 (0.052 g, 28%), $[\alpha]_D = +46.4$ ($c = 1.47$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 0.14$ (s, 9H), 2.65–2.76 (m, 2H), 3.00–3.18 (m, 2H), 4.18–4.30 (m, 2H); and

9 (0.0939 g, 37%), $[\alpha]_D = +58.6$ ($c = 2.23$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 0.12$ (s, 18H), 2.60–3.05 (m, 4H), 4.08–4.12 (m, 2H).

Synthesis of (R)-3-Acetoxy-(R)-4-hydroxythiolane **10** *and (R,R)-3,4-Diacetoxythiolane* **11**

To a solution of **6** (0.694 g, 5.7 mmol) in methylene chloride (15 mL) $Yb(OTf)_3$ was added (0.342 g, 0.551 mmol) followed by Ac_2O (0.54 mL, 0.581 g, 5.7 mmol). The mixture was stirred at room temperature (TLC control: ethyl acetate–hexane 2:1). The solvent was evaporated and the residue was purified by column chromatography using AcOEt–hexane 1:20 to AcOEt–hexane 2:1 as solvent to give:

10 (0.497 g, 54%), $[\alpha]_D = +72.9$ ($c = 1.37$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.05$ (s, 3H), 2.76–3.28 (m, 4H), 4.30–4.41 (m, 1H), 5.16–5.21 (m, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 21.01$, 33.13, 36.27, 76.34, 80.04, 170.48; and

11 (0.204 g, 18%), $[\alpha]_D = +112.0$ ($c = 2.04$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.08$ (s, 6H), 2.85–3.33 (m, 4H), 5.29–5.41 (m, 2H). ^{13}C NMR ($CDCl_3$): $\delta = 20.96$, 33.75, 77.62, 169.80.

Synthesis of (R)-3-Benzyloxy-(R)-4-hydroxythiolane **12** *and (R,R)-3,4-Dibenzyloxythiolane* **13**

A solution of **6** (0.0513 g, 0.428 mmol) in THF (3 mL) was cooled to 0°C and a natrium hydride dispersion 50–60% in oil (0.0206 g, 0.860 mmol) was added. After 5 min Bu_4NI (a few milligrams) and benzyl bromide (0.0728 g, 0.428 mmol) were added. The mixture was stirred at room temperature for 5 days. Although TLC control (hexane–ethyl acetate 2:1) revealed that a substantial amount of the substrate was still present, the mixture was filtered through Celite. After evaporation of the solvent the residue was purified by preparative TLC using hexane–ethyl acetate 2:1 as solvent to give:

12 (0.0141 g, 15%), $[\alpha]_D = +70.7$ ($c = 1.41$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.95$ (s, 1H), 2.70–3.20 (m, 4H), 4.01–4.07 (m, 1H), 4.34–4.40 (m, 1H), 4.50–4.69 (m, 2H). MS (CI): m/z 211 (M+1); and

13 (0.0180 g, 14%), $[\alpha]_D = +82.6$ ($c = 0.90$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.73$–3.19 (m, 4H), 4.01–4.07 (m, 1H), 4.31–4.40 (m, 1H), 4.50–4.70 (m, 4H), 7.13–7.44 (m, 10H). MS (CI): m/z 301 (M+1).

Synthesis of (R)-3-Tosyloxy-(R)-4-hydroxythiolane **14** *and (R,R)-3,4-Ditosyloxythiolane* **15**

To a solution of **6** (0.110 g, 0.916 mmol) in methylene chloride (5 mL) were added tosyl chloride (0.175 g, 0.916 mmol) and triethylamine (0.092 g, 0.916 mmol). The mixture was stirred at room temperature until the substrates were completely consumed (TLC control: hexane–ethyl acetate 2:1). The solvent was evaporated and residue was purified by preparative TLC using ethyl acetate–hexane 2:1 as solvent to give:

14 (0.1156 g, 46%), $[\alpha]_D = +38.6$ ($c = 3.47$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.28$ (s, 1H), 2.45 (s, 3H), 2.78–3.16 (m, 4H), 4.40–4.46 (m, 1H), 4.85–4.91 (m, 1H), 7.34–7.83 (m, 4H). MS (CI): m/z 275 (M+1); and

15 (0.1412 g, 36%), $[\alpha]_D = +13.0$ ($c = 0.54$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.47$ (s, 6H), 2.77–3.20 (m, 4H), 4.99–5.01 (m, 4H), 7.27–7.81 (m, 4H).

Synthesis of (R)-3-Acetoxy-(R)-4-hydroxythiolane-1-oxides **16**

To a solution of **10** (0.100 g, 0.617 mmol) in acetonitrile (3 mL) was added PhIO (0.136 g, 0.617

mmol) and montmorillonite K 10 (0.136 g). The mixture was stirred at room temperature until the substrate was completely consumed (TLC control: ethyl acetate–methanol 9:1). After filtration through Celite and evaporation a crude reaction mixture was obtained (0.112 g, 100%, *trans* : *cis* 3:2). Preparative TLC (AcOEt–MeOH 9:1) gave the pure compound **16** (0.033 g, 30%) as 7:1 diastereomer mixture with *trans* **16** prevailing.

^{1}H NMR (CD_3OD): $\delta = 2.01$ (s, 3H), 2.11 (s, 3H), 2.89–3.63 (m, 4H), 3.94 (s, 1H), 4.68–4.71 (m, 1H), 4.80–4.83 (m, 1H), 5.27–5.33 (m, 1H), 5.72–5.78 (m, 1H). The peaks characteristic of the prevailing trans diastereomer are underlined.

*Synthesis of (R)-3-Acetoxy-(R)-4-hydroxythiolane 1-(S)-oxide cis-***16**

A mixture of **7** (0.050 g, 0.367 mmol), lipase AK (ca. 10 mg), and vinyl acetate (0.5 mL) in $CHCl_3$ was stirred at room temperature until the substrate was completely consumed (AcOEt–MeOH 9:1). Then the enzyme was filtered off and the solvent was evaporated under vacuum. The residue was purified by column chromatography using ethyl acetate–methanol 20:1 to ethyl acetate–methanol 9:1 as solvent, to give *cis*-**16** (0.042 g, 65%) $[\alpha]_D = +62.58$ ($c = 1.51$, $CHCl_3$.); ^{1}H NMR ($CDCl_3$.): $\delta = 2.11$ (s, 3H), 2.90–3.62 (m, 5H), 4.80–4.83 (m, 1H), 5.29–5.32 (m, 1H).

Synthesis of (R,R)-3,4-Diacetoxythiolane-1-oxide **17**

To a solution of **11** (0.185 g, 0.907 mmol) in acetonitrile (5 mL) was added PhIO (0.199 g, 0.907 mmol) and montmorillonite K 10 (0.199 g). The mixture was stirred at room temperature until the substrate was completely consumed (TLC control: ethyl acetate–methanol 9:1). After filtration through Celite and evaporation the crude reaction mixture was purified by column chromatography using AcOEt–MeOH 30:1 to AcOEt–MeOH 9:1 as eluent to give **17** (0.199 g, 100%), $[\alpha]_D = +81.29$ ($c = 1.08$, $CHCl_3$).

^{1}H NMR ($CDCl_3$): $\delta = 2.05$ (s, 3H), 2.13 (s, 3H), 3.00–3.58 (m, 4H), 3.42–3.47 (m, 1H), 5.71–5.77 (m, 1H). MS (CI): m/z 221 (M+1).

Synthesis of meso-3,4-Dihydroxythiolane **18**

A mixture of 1,4-ditosyl-*meso*-threitol obtained in an analogous way as **5**, (7.089 g, 0.016 mol) and $Na_2S{\cdot}9H_2O$ (10.023 g, 0.042 mol) in EtOH (140 mL) was refluxed for 5 h (TLC control: ethyl acetate–hexane 2:1). After filtration through Celite and evaporation the residue was dissolved in $CHCl_3$. The precipitate was filtered off and washed with a large amount of $CHCl_3$. The solvent was removed under vacuum and the residue was purified by column chromatography, using $CHCl_3$ to $CHCl_3$–MeOH 10:1 (in gradient) as solvent to give **18** (1.286 g, 65%).

^{1}H NMR (CD_3OD): $\delta = 2.70$–2.95 (m, 4H), 4.13–4.20 (m, 2H).

Synthesis of cis-3-Acetoxy-4-hydroxythiolanes **19**

Method A. A mixture of **18** (0.1 g, 0.833 mmol), a lipase (ca. 10 mg), and vinyl acetate (0.5 mL) in i-Pr_2O was stirred overnight at room temperature. Then the enzyme was filtered off and the solvent was evaporated under vacuum. The residue was purified by column chromatography using ethyl acetate–hexane 1:20 to ethyl acetate–hexane 1:5 as solvent, to give **19** (0.110 g, 81%) $[\alpha]_D = -13.7$ ($c = 1.35$, $CHCl_3$.).

^{1}H NMR ($CDCl_3$.): $\delta = 2.13$ (s, 3H), 2.30 (br.s, 1H), 2.81–3.15 (m, 4H), 4.39–4.49 (m, 1H), 5.15–5.38 (m, 1H).

HRMS (CI): calc. for $C_6H_{11}SO_3$ $m/z =$ 163.042892, found $m/z = 163.0433$.

Method B. A mixture of **20** (0.0945 g, 0.460 mmol) and a lipase (ca. 10 mg) in a i-Pr_2O (5 mL) saturated with a phosphate buffer (pH 7.2) was stirred overnight at room temperature. Then anhydrous magnesium sulfate was added to remove water. The precipitates were filtered off, the solvents were removed under vacuum, and the residue was purified by column chromatography using ethyl acetate–hexane 1:20 to ethyl acetate–hexane 1:5 as solvent, to give **19** (0.021 g, 28%), $[\alpha]_D = +2.85$ ($c = 0.74$, $CHCl_3$.).

^{1}H NMR ($CDCl_3$.): $\delta = 2.13$ (s, 3H), 2.30 (br.s, 1H), 2.81–3.15 (m, 4H), 4.39–4.49 (m, 1H), 5.15–5.38 (m, 1H).

Synthesis of meso-3,4-Diacetoxythiolane **20**

To a solution of **18** (0.1 g, 0.833 mmol) in dichloromethane (5 mL) $Yb(OTf)_3$ was added (0.045 g, 0.072 mmol) followed by Ac_2O (0.24 mL, 0.256 g, 2.498 mmol). The mixture was stirred at room temperature until the substrate was completely consumed (TLC control: ethyl acetate–hexane 2:1). The reaction mixture was washed with water, aqueous saturated $NaHCO_3$ solution and water. The organic layer was dried over anhydrous magnesium sulfate. The precipitate was filtered and the solvent was evaporated. The residue was purified by column chromatography using chloroform as solvent to give **20** (0.154 g, 90%).

^{1}H NMR ($CDCl_3$): $\delta = 2.07$ (s, 3H), 2.86–3.14 (m, 4H), 5.33–5.41 (m, 2H). ^{13}C NMR ($CDCl_3$): $\delta = 20.85$, 30.74, 74.01, 170.11. MS (CI): m/z 205 (M+1).

Synthesis of (3S,4R)-3-Acetoxy-4-hydroxythiolane-1-oxides **21**

To a solution of (−)-19 (0.3 g, 1.852 mmol) in acetonitrile (10 mL) was added PhIO (0.407 g, 4.852 mmol) and montmorillonite K 10 (0.407 g). The mixture was stirred at room temperature until the substrate was completely consumed (TLC control: ethyl acetate–methanol 9:1). After filtration and evaporation the crude reaction mixture was purified by column chromatography using AcOEt–MeOH 20:1 to AcOEt–MeOH 9:1 as eluent to give: **21b** (0.058 g) as an oil.

^{1}H NMR ($CDCl_3$): $\delta = 2.14$ (s, 3H), 2.89–3.67 (m, 4H), 4.64–4.70 (m, 1H), 5.12–5.21 (m, 1H), ^{13}C NMR ($CDCl_3$): $\delta = 20.76$, 55.47, 73.74, 75.02, 170.39. MS (CI): m/z 179 (M+1).

(1*S*, 3*S*, 4*R*)-**21a** (0.0255 g), mp. 101–103°C, $[\alpha]_D = -0.51$ ($c = 2.55$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.13$ (s, 3H), 2.94–3.44 (m, 4H), 4.91–4.98 (m, 1H), 5.66–5.75 (m, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 20.82$, 30.87, 54.50, 57.83, 72.06, 75.02, 169.98. MS (CI): m/z 179 (M+1) and an inseparable mixture of both diastereomers of **21** (0.119 g). Total yield 62%.

Synthesis of (S,S)-3,4-Diacetoxythiolane **11***—Chemical Correlation Using Mitsunobu Reaction*

To a solution of **19** (0.0709 g, 0.4376 mmol), triphenylphosphine (0.1965 g, 0.75 mmol), and diethyl azodicarboxylate (0.147 mL, 0.1515 g, 0.75 mmol) in THF (3 mL) was added acetic acid (0.042 mL, 0.045 g, 0.75 mmol) at −78°C. The resulting solution was stirred at this temperature for 1.5 h and then was allowed to reach room temperature and stirred for 12 h. Then the solvent was evaporated. The residue was purified by flash chromatography using ethyl acetate–hexane 1:10 as eluent to give product **11** (0.0061 g, 7%), $[\alpha]_D = -15.1$ ($c = 0.61$, $CHCl_3$).

^{1}H NMR ($CDCl_3$): $\delta = 2.05$ (s, 3H), 2.76–3.28 (m, 4H), 4.30–4.41 (m, 1H), 5.16–5.21 (m, 1H).

General Procedure of Asymmetric Addition of Et_2Zn to Benzaldehyde

A catalyst (0.1 mmol) and benzene (10 mL) were placed in a flask. To ensure dryness some benzene was distilled off. To this solution a solution of Et_2Zn (1 M in hexane solution) (3 mmol) was added under argon at 0°C. After stirring for 0.5 h benzaldehyde (1 mmol) was added at 0°C, and the reaction mixture was stirred for 2 h at 0°C, then overnight at room temperature. Then it was treated with 5% cold aqueous HCl solution. The layers were separated and the water layer was extracted with diethyl ether (4 × 5 mL). The combined organic extracts were washed with brine (10 mL) and dried over anhydrous magnesium sulfate. After filtration and evaporation the residue was purified by preparative TLC using hexane–ethyl acetate 5:1 as solvent to give optically active 1-phenylpropan-1-ol **22**.

TABLE 2 Crystal Data and Experimental Details of **21a**

Molecular formula		$C_6H_{10}O_4S$
Formula weight		178.20
Crystallographic system		*Pna*2$_1$
Space group		Orthorhombic
a (Å)		9.118(2)
b (Å)		9.701(2)
c (Å)		9.243(2)
V (Å^3)		817.6(3)
Z		4
D_c (g/cm^3)		1.448
μ (mm^{-1})		3.294
Crystal dimensions (mm)		0.10 × 0.12 × 0.32
Maximum 2θ (°)		150
Radiation, λ (Å)		Cu Kα, 1.54178
Scan mode		$\omega/2\theta$
Scan width (°)		0.65 + 0.14tanθ
hkl ranges:	*h* =	0 11
	k =	−12 12
	l =	0 11
DECAY correction:	min.	1.00002
	max.	1.01098
	ave.	1.00544
EAC correction:	min.	0.8950
	max.	0.9993
	ave.	0.9548
No. of reflections: unique		898
with $I > 0\sigma(I)$		881
obs. with $I > 0\sigma(I)$		851
No. of parameters refined		141
Largest diff. peak (eÅ^{-3})		0.296
Largest diff. hole (eÅ^{-3})		−0.203
Shift/esd max.		0.000
R_{obs}		0.0280
wR_{obs}		0.0805
S_{obs}		1.052
weighting coeff.[a]	*m*	0.055800
	n	0.107500
extinction coeff.[b]	*k*	0.0040(9)
R_{int}		0.0201
T_{meas}		293(2)
F(000)		376

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

Crystallographic Data of **21a**

Crystal and molecular structure of **21a** was determined using data collected at room temperature on a CAD4 diffractometer. Crystal data and experimental details are shown in Table 2. The lattice constants were refined by least-squares fit of 25 reflections in the θ range 17.00–32.64°. The decline in intensities of three control reflections (4,1,2; 1,0,−4; 3,−1,−5) was −2.2% during 25.3 h of exposure time, the intensity corrections was applied (DECAY program) [20]. An empirical absorption correction was applied by the use of the ψ-scan method (EAC program) [20,21]. A total of 881 observed reflections with $I > 0\sigma(I)$ were used to solve the structure by direct methods and to refine it by full matrix least-squares [22,23] using F^2. Hydrogen atoms were found on difference Fourier map and refined isotropically. Anisotropic thermal parameters were refined for all non-hydrogen atoms. The final refinement converged to $R = 0.028$ for 141 refined parameters and 851 observed reflections with $I > 2\sigma(I)$ with inclusion of extinction parameter into refinement (the obtained value of extinction parameter was 0.0040(9)). The absolute configurations at the chiral atoms were established as S_S, S_{C3}, R_{C4}. The absolute structure was determined by the Flack method [24] with result $\chi = 0.01(3)$. Data corrections were carried out with the Enraf-Nonius SPD crystallographic computing package [20]; structure solution SHELXS [22]; structure refinement SHELXL [23]. The authors have deposited all crystallographic data for this structure with the Cambridge Crystallographic Data Centre [25].

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[25] Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number 244831. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).