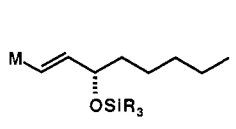
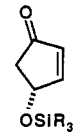
synthetic intermediate **12**[14] was obtained in 71% yield. No cyclopentenones corresponding to the β-siloxy ketone **11** or **12** were formed. The present procedure thus results in considerable simplification of the PG synthesis; particularly isolation of the product is much easier than in our earlier synthesis using a phosphine-complexed organocopper reagent and triphenyltin chloride.[14b,c,18,19]



7, M = $Sn(n\text{-}C_4H_9)_3$
8, M = Li



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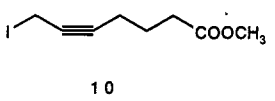

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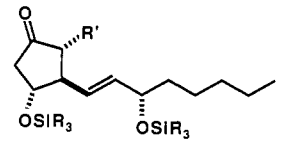

11, R' = H
12, R' = $CH_2C{\equiv}C(CH_2)_3COOCH_3$

SiR_3 = $Si(CH_3)_2$-*tert*-C_4H_9

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Supplementary Material Available: Experimental procedures and spectroscopic data for the new compounds (10 pages). Ordering information is given on any current masthead page.

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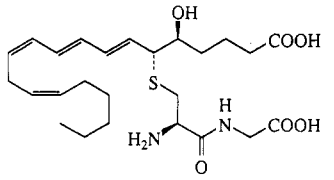
(19) Product **12** was most conveniently separated from unreacted **10** on preparative high-performance liquid chromatography using a Japan Analytical Industry Model LC-09 chromatograph (column, JAIGEL AJ2H × 2; eluant, $CHCl_3$; flow rate, 3.5 mL/min; detection UV-254H and RI-2).

Synthesis of Chiral Dithioacetals: A Chemoenzymic Synthesis of a Novel LTD_4 Antagonist

Summary: An enantioselective enzymatic hydrolysis of prochiral diester **3**, having four bonds between the prochiral center and ester group, serves as the key step in a short and efficient synthesis of both enantiomers of the selective LTD_4 antagonist, MK-0571.

Sir: Aryl and alkyl dithioacetals of mercaptopropionic acid derivatives are potent receptor antagonists of leukotriene D_4 (**1**) and are being developed as therapeutic agents for bronchial diseases.[1] One of the most promising candidates currently in clinical trials is MK-0571 (**2a**), a racemic compound. Due to the similarity of the two thioalkyl side chains, attempts to resolve **2a** by classical methods, such as crystallization of diastereomeric salts or chromatographic separation of diastereomeric derivatives, proved difficult. Recently, the synthesis of both enantiomers of **2a** and analogues has been reported.[2] This synthesis entails chromatographic separation of a 50/50 mixture of diastereomers early in the synthesis followed by transformation of each diastereomer into the appropriate enantiomer. However, scale up of such a process would be difficult. Thus, we directed our efforts to enzymatic resolutions, resulting in a straightforward route to both enantiomers of **2a**, described herein.



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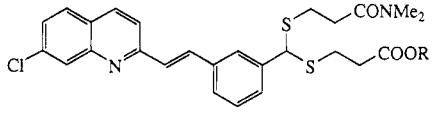

2 (a) R = H
(b) R = Me

There is little or no literature precedent[3] for enzymatic resolutions of compounds such as **2**, wherein there is a 4-bond distance between carboxylic acid and the chiral center, and the thioalkyl chains are similar and have unrestricted conformational flexibility. Nonetheless, two enzymatic approaches were examined: (1) selective hydrolysis of racemic esters of **2a** and (2) hydrolysis of prochiral diesters **3**. Several enzymes were screened with a variety of esters before finding that lipase from *Pseudomonas* species cleanly hydrolyzed the Me and CH_2CONH_2 prochiral diesters **3a** and **3b** with >98% enantiomeric excess and 90% yield.[4-6] Over hydrolysis to the diacid

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(4) The enantiomeric ratios were determined by HPLC analysis of samples derivatized with (*R*)- or (*S*)-1-(1-naphthyl)ethylamine. For **4a**, HPLC conditions were: Zorbax C8 column, 25 cm; eluent consisting of 80:20 CH_3CN–0.1% aqueous H_3PO_4; flow 2.0 mL/min; ambient temperature; detection at 350 nm. The two diastereomeric amides elute at 25 and 27 min with base-line resolution. When the amides are prepared with (*R*)-1-(1-naphthyl)ethylamine, the diastereomer from (*R*)-**4a** elutes first. The amides prepared from **2a** elute at similar times under these conditions. The rotations of both enantiomers of **2a** were identical with those reported in ref 2b. ^1H NMR spectral data of the enantiomers match those of racemic material reported in ref 9.

(5) These results are with purified *Pseudomonas* lipase from Sigma. With crude lipase from Amano Enzyme Co., the ee was 95%, the chemical yield was 85%, and 5% diacid was formed from the prochiral dimethyl ester. With pure lipase from Beohringer-Mannheim, no reaction occurred.

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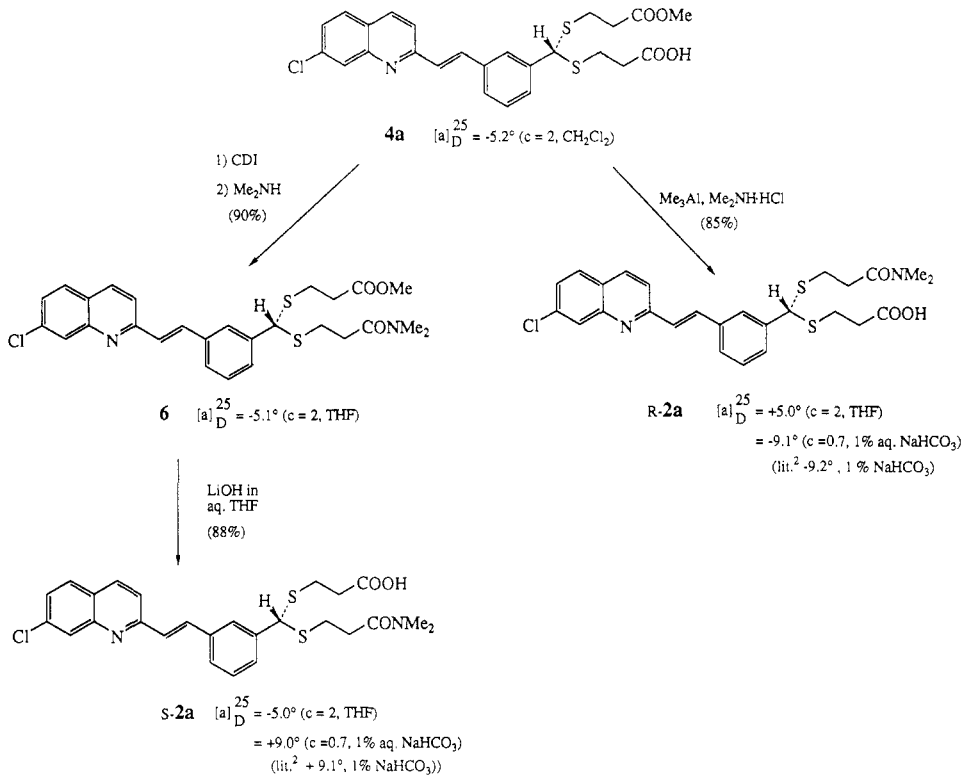
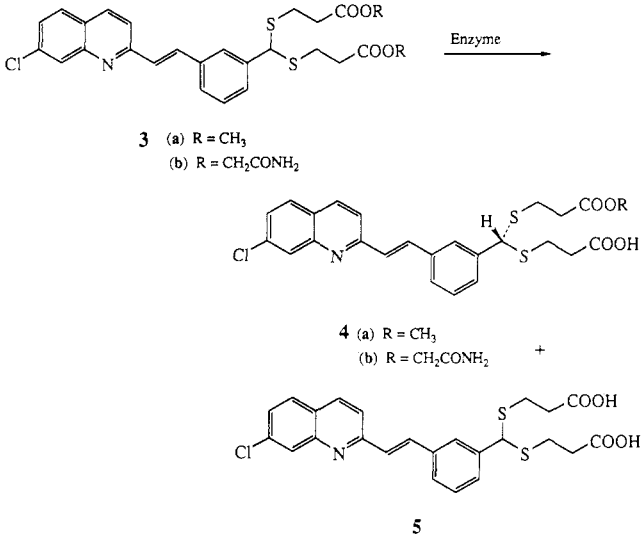
Scheme I



occurred to the extent of only 0.5% with the Me ester and 3% with the CH_2CONH_2 ester.



With chemically and optically pure half methyl ester **4a** available, we were able to readily convert it into each enantiomer of MK-0571 (**2a**), as shown in Scheme I.[7] The *R* isomer was prepared by reacting the half ester **4a** with $Me(Cl)AlNMe_2$ (Weinreb's reagent).[8] The *S* isomer was prepared by reacting half ester **4a** sequentially with CDI and Me_2N to give amide–ester **6**, which was then hydrolyzed with LiOH in THF.

Far less satisfactory results were obtained by enzymatic hydrolysis of the racemic esters of **2**. Eight esters of **2** were prepared (R = Me, allyl, CH_2COOEt, CH_2CH_2OMe, CH_2COPh, CH_2CONH_2, CH_2CONMe_2, and CH_2CN) and screened with several enzymes. The best result was obtained using lipase from *Candida cylindracea* with the CH_2CONEt_2 ester, which gave a 65% ee (enriched in the *R* isomer) with a 30% chemical yield. This material could not be enantiomerically purified by recrystallization.

In summary, we have demonstrated a short and efficient route to both enantiomers of the promising LTD_4 antagonist MK-0571 based on a chiral enzymatic hydrolysis of a prochiral diester. This work also shows the power of chiral enzymatic hydrolyses in that differentiation by the enzyme occurs even though the prochiral center is four bonds away from the ester group. Extensions to analogues having variable chain lengths are in progress.

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(6) Typical experimental conditions for the enzymatic hydrolysis are as follows: Dimethyl ester **3a** (1.02 g), lipase from *Pseudomonas* sp. (Sigma) (4.2 mg), and Triton X-100 (5.1 g) were stirred vigorously in 100 mL of 0.1 M phosphate buffer (pH 7) for 48 h at 40 °C. After concentration to 60 mL and cooling to 0 °C, 0.91 g of crystalline **4a** was isolated (92%): mp 121–122 °C; ^1H NMR (CD_3CN) δ 2.54–2.61 (m, 4 H, CH_2), 2.73–2.87 (m, 4 H, CH_2), 3.61 (s, 3 H, CO_2CH_3), 5.12 (s, 1 H, Ar-CH), 7.38–8.26 (m, 11 H, olefinic/aromatic), 9.2 (broad s, 1 H, CO_2H). Anal. Calcd for $C_{25}H_{24}ClNO_4S_2$: C, 59.81; H, 4.82; N, 2.79; Cl, 7.06; S, 12.77. Found: C, 59.75; H, 4.92; N, 2.73; Cl, 7.00; S, 12.69.

(7) The absolute stereochemistry has been determined by an X-ray crystal structure of an intermediate. See ref 2b.

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