ORGANIC LETTERS

2000
Vol. 2, No. 23
3531−3534

Epoxidation of *p*-Methoxycinnamates Using Chiral Dioxiranes Derived from New Trisubstituted Halogenated Cyclohexanones: Enhanced Efficiency of Ketones Having an Axial Halogen

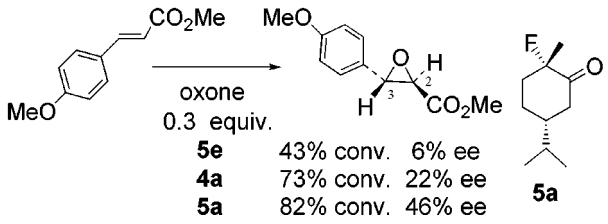
A. Solladié-Cavallo*,† and L. Bouérat

Laboratoire de Stéréochimie Organométallique associé au CNRS, ECPM/Université Louis Pasteur, 25 rue Becquerel, 67087 - Strasbourg Cedex 2, France

ascava@ecpm.u-strasbg.fr

Received June 29, 2000 *(Revised Manuscript Received October 16, 2000)*

ABSTRACT



Epoxidation of *p*-methoxycinnamates using substoichiometric amounts of chiral and enantiopure dioxiranes generated in situ from chiral trisubstituted chloro and fluoro cyclohexanones showed that ketones with an *axial* Cl or F were more efficient than ketones with an *equatorial* Cl or F, that increasing the steric hindrance in the α-position (isopropyl instead of methyl) decreased the efficiency, and that the α-fluoro ketone 5a (axial fluorine) was the most efficient (82% conversion and 46% ee in (–)-epoxide).

Dioxiranes generated *in situ* from oxone and chiral ketones have been shown to be remarkably promising oxidizing reagents for the asymmetric epoxidation of olefins.[1] However, most of the dioxiranes generated from chiral ketones reported in the literature are unreactive toward electron-poor olefins. Only recently were three examples of asymmetric epoxidation of alkyl cinnamates proposed. While monofluorinated ketone **1a** provided epoxidation of methyl styrene with 100% conversion and 35% ee,[2a] the α-fluorinated ketone **1b** (0.25 equivalent) provided epoxidation of methyl cinnamate with ∼33% yield and 64% ee[2b] and epoxidation of ethyl cinnamate using the ketones **2a** and **2b**, derived from (−)-quinic acid, led to ∼34% yield with 86% ee and ∼35% yield with 89% ee, respectively.[3]

These reports prompted us to publish our first results concerning the epoxidation of methyl *p*-methoxycinnamate

† Tel. 00 33 3 88 13 69 79. Fax 00 33 3 88 13 69 13.

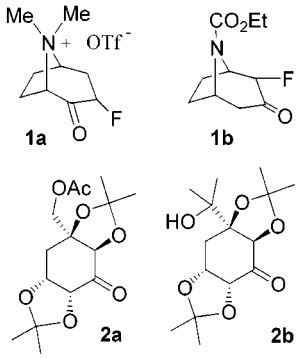
(1) (a) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491−492. (b) Wang, Z. X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328−2329. (c) Tu, Y.; Wang, Z. X.; Shi, Y. *J Am. Chem. So* **1996**, *118*, 9806−9807. For further information, see the following review: (d) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847−859.

(2) (a) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem*. **1997**, *62*, 8288−8289. (b) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621−622.

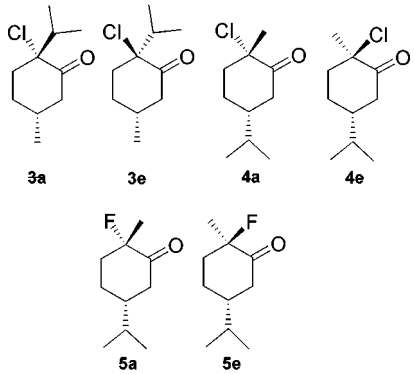
(3) Wang, Z. X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443−6458.

(4) Solladié-Cavallo, A.; Bouérat, L. *Tetrahedron: Asymmetry* **2000**, *11*, 935−941. Ketone **4a** has already been prepared and tested to study effects of remote substituents on catalytic asymmetric epoxidation. Cf. Yang D.; Yip Y. C.; Chen J.; Cheung K. K. *J. Am. Chem. Soc*. **1998**, *120*, 7659−7660.

10.1021/ol0001721 CCC: $19.00 © 2000 American Chemical Society
Published on Web 10/24/2000

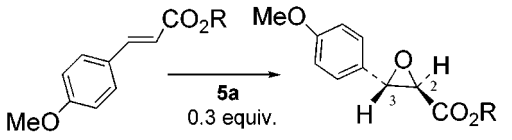


6a, *tert*-butyl *p*-methoxycinnamate **6b**, and *trans*-stilbene using the α-halogenated ketones **3**, **4**, and **5** which were



synthesized in two to three steps from natural products (Scheme 1).[4]

Scheme 1



convers. ee

6a R = Me : Method **A**, **7a** (-)-(2*R*,3*S*) 97% 40%
: Method **B**, **7a** (-)-(2*R*,3*S*) 82% 46%
6b R = tBu : Method **A**, **7b** (-)-(2*R*,3*S*) 97% 33%

The ketones **3** to **5** have been used in substoichiometric amounts (0.1 or 0.3 equiv) by following two different procedures: **A** (Table 1),[5a] addition of a 0.42 M solution of oxone, 3 equiv, during 6 h to a 0.05 M solution of olefin in dioxane/H_2O [5b] (pH 8.5−9); **B** (Table 2),[5c] addition of a 0.34 M solution of oxone, 1.4 equiv, during 8 h to a 0.08 M solution of olefin in DME/H_2O [5b] (pH 8.5−9).

Table 1. Epoxidation of Methyl 4-Methoxycinnamate **6a** Following Procedure A[5] and Using Ketones **3**−**5**

	X	ketone	equiv of ketone	starting dioxane/H_2O	react. time (h)	react. temp.	convn (%)[a]	ee (%)[b,c]
1			0	3/2	6	amb.	15	
2	Cl	**3e**	0.3	3/2	6	amb.	14	2 (−)
3	Cl	**3a**	0.3	3/2	6	amb.	24	2 (−)
4	Cl	**4e**	0.3	3/2	6	amb.	20	5 (−)
5	Cl	**4a**	0.3	3/2	6	amb.	73	22 (−)
6	Cl	**4a**	0.3	3/2	6	0 °C	22	43 (−)
7	F	**5e**	0.3	3/2	6	amb.	43	6 (+)
8	F	**5a**	0.3	3/2	6	amb.	99	40 (−)
9	F	**5a**	0.3	3/2	6	0 °C	97	37 (−)
10	F	**5a**	0.1	3/2	6	amb.	83	38 (−)

[a] Determined by ^{1}H NMR 200 MHz. [b] Determined by chiral HPLC (chiralcel OG). [c] The sign of the optical rotation of the *major* enantiomer is given in parentheses.

Table 2: Epoxidation of Methyl 4-Methoxycinnamate **6a** Following Procedure B[5] and Using Ketone **5a**

	ketone	equiv of ketone	equiv of PTA[a]	Na_2EDTA[b]	react. time (h)	react. temp.	convn (%) [c]	ee (%)[d,e]
1	**5a**	0.1	0.04	yes	8	0 °C	65	44 (−)
2	**5a**	0.1	0	yes	8	0 °C	68	45 (−)
3	**5a**	0.1	0	no	8	0 °C	71	46 (−)
4	**5a**	0.1	0	no	8	amb.	67	40 (−)
5	**5a**	0.3	0	no	8	0 °C	82	46 (−)

[a] PTA (phase transfert agent): $Bu_4N^+HSO_4^-$ was added in the olefin/ketone solution. [b] The aqueous Na_2EDTA solution (4×10^{-4} M, 3.2 mL) was used to dissolve the oxone. [c] Determined by ^{1}H NMR 200 MHz. [d] Determined by chiral HPLC. [e] The sign of the optical rotation of the *major* enantiomer is given in parentheses.

The roles of Na_2EDTA and $[Bu_4N]HSO_4$ have been studied, and it was found that conversions and ee % were not affected by the presence or absence of these additives (Table 2, lines 1, 2, and 3).

For all reactions, the percentages of conversion have been determined by combining weight and ^{1}H NMR of solvent-free crude products; then the epoxide[6] was isolated by flash

(5) (a) **Procedure A.** Distilled water (6 mL) and a solution (4 mL) of acetic acid (0.5 mL) and 0.1 M aqueous K_2CO_3 (100 mL) are added under stirring to a solution of 1 mmol of methyl *p*-methoxycinnamate **6a** (0.192 g, 1 equiv) and 0.1 or 0.3 mmol of ketone (0.1 or 0.3 equiv) in dioxane (16 mL). The mixture is cooled to the desired temperature, and a solution of oxone (1.850 g, 3 mmol, 6 equiv of oxidant) in distilled water (7 mL) is added dropwise over 6 h. During addition of oxone, the pH is controlled and regulated (~8.5−9) by addition of a solution of 1 M K_2CO_3. The reaction is immediately quenched by addition of CH_2Cl_2 (30 mL) and water (10 mL). The mixture is extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, and analyzed. (b) CH_3CN/H_2O gave lower percentages of conversion than dioxane/H_2O and DME/H_2O. (c) **Procedure B.** A solution (6 mL) of acetic acid (0.5 mL) and 0.1 M aqueous K_2CO_3 (100 mL) is added under stirring to a mixture of 0.8 mmol of methyl *p*-methoxycinnamate **6a** (0.154 g, 1 equiv) and ketone **5a** (0.08 mmol, 0.1 equiv or 0.24 mmol, 0.3 equiv) dissolved in dimethoxyethane (DME, 10 mL). The mixture is cooled to the desired temperature and a solution of oxone (0.68 g, 1.1 mmol, 2.8 equiv of oxidant) in distilled water (3.2 mL) is added dropwise over 8 h. During addition of oxone, the pH is controlled and regulated (~8.5−9) by addition of a solution of 1.4 M K_2CO_3. The reaction is immediately quenched by adding CH_2Cl_2 (30 mL) and water (10 mL). The mixture is extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, and analyzed.

(6) Stilbene oxide and epoxide **7a** obtained exhibit spectra identical with those of the racemic compounds purchased from Aldrich. IR and ^{1}H and ^{13}C NMR of epoxide **7b** were identical to those in the literature, cf. Adger, B. M.; Barkley, J. V.; Bergeron, S.; Cappi, M. W.; Flowerdew, B. E.; Jackson, M. P.; McCague, R.; Nugent, T. C.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3501−3507. This paper, **7a**: HPLC, 40% ee, $[\alpha]_D = -77$ ($c = 0.5$, MeOH); lit. ~100% ee, $[\alpha]_D = -212$ ($c = 0.5$, MeOH). For

chromatography on silica gel. The ee % were determined by HPLC (Chiralcel OD and OG columns). [7]

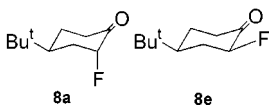
As expected, when the concentration of ketone increased (0.1 to 0.3 equiv) the percentage of conversion increased (Tables 1 and 2). The temperature effect depended on the ketone (Table 1, compare lines 5/6 and 8/9) and on the conditions (compare Table 1, lines 8/9 and Table 2, lines 3/4) and is thus difficult to predict.

α-Chloro ketones **3e** and **3a** with an isopropyl group in the α position led to low conversion in epoxide (respectively 14% and 24%, Table 1, entries 2 and 3).

When the epoxidation was carried out with the α-chloro ketones **4e** and **4a**[4] having a methyl group in the α-position instead of an isopropyl group, the *axial* or *equatorial* position of the chlorine had a dramatic effect on the efficiency of the ketone, with a significant enhancement of the efficiency of the ketone when the chlorine is *axial*: 73% conversion with the α-chlorine *axial* compared to 20% conversion with the α-chlorine *equatorial* (Table 1, lines 5 and 4). The same behavior was observed with the α-fluoro ketones **5e** and **5a**. When the α-fluorine is in the *axial* position (**5a**), almost full conversion was observed while in the *equatorial* position (**5e**) the conversion was only 43% (Table 1, lines 8 and 7). It thus appears that the ketones having an *axial* halogen (Cl or F) are more efficient than those having an *equatorial* one.

Although the observed efficiency of these ketones is the result of several competing factors (the rate of formation of the Criegee intermediate, its evolution toward the dioxirane or toward the lactones, the reaction of the dioxirane with the alkene), it is interesting to note that recent B3LYP/6-31G* calculations of transition states of ethylene epoxidation by dioxiranes derived from fluorocyclohexanones predicted that the *axial*-substituted ketone should be more reactive than the *equatorial* one.[8]

However, it has been recently observed[2a] that α-fluoro-4-*tert*-butylcyclohexanone **8e**, which has an *equatorial* fluorine, was more efficient (70% conversion after 10 h) than ketone **8a**, which has an *axial* fluorine (20% conversion after 10 h) for epoxidation of 1-benzyloxy-4-hexene while an ^{1}H NMR study of the electrophilic reactivity of these α-fluoro ketones **8** toward methanol-d_4 showed that solvation was larger for **8a** (100%) than for **8e** (65%).



8a **8e**

A similar ^{1}H NMR study of the solvation equilibria with methanol-d_4 of the ketones **4a**, **5e**, and **5a** was thus carried out. It was found that no hemiketal was formed in the case of α-chloro ketone **4a**. In the case of α-fluoro ketone **5a**, having an *axial* fluorine, 50% of the hemiketal (both diastereomers) was formed and the equilibrium was reached after 1 h, while only 22% of the hemiketal (both diastereomers) was formed in the case of α-fluoro-ketone **5e**, having an *equatorial* fluorine, and the equilibrium was also reached after 1 h. It thus appears that the order of electrophilic reactivities toward methanol-d_4 is **5a** > **5e** ≫ **4a**, while the order of efficiency toward epoxidation is **5a** > **4a** > **5e**. In light of the 73% conversion (Table 1, line 5) obtained with ketone **4a**, it seems that the 0% solvation by methanol-d_4 does not reflect the electophilic reactivity of this ketone toward oxone, although it could well reflect the electrophilic reactivity toward water.[2a]

However, the general trend is the same for ketones **5** and α-fluoro-4-*tert*-butylcyclohexanones **8**, as, in both cases, an *axial*-fluorine appears to be better than an *equatorial*-fluorine in promoting the electrophilic reactivity of the carbonyl toward methanol-d_4 solvation: **5a** = 50% and **5e** = 22%; **8a** = 100% and **8e** = 65%, all at equilibrium. It is also worth noting that, quite similar to that of ketone **8a**[1d,2a] (which rapidly decomposed through Baeyer−Villiger oxidation under the epoxidation conditions), ketone **5a** underwent Baeyer−Villiger oxidation but not under all the conditions used,[9] while **5e**, as was **8e**, was stable under the epoxidation conditions.

Concerning the enantioselectivity, it appears that only ketones **4a** and **5a** which have an *axial* halogen provide significant ee (Table 1, lines 6, 8, 9, and 10). When epoxidation was carried out by following procedure **A** without ketone, 15% of direct epoxidation of the olefin by oxone was observed[10] (Table 1, line 1). This suggests that the direct epoxidation might compete but mainly when ketones of low activity are involved and may therefore be responsible for the very low ee obtained with the ketones **3e**, **3a**, **4e**, and **5e**.

Experiment 10 (Table 1) using 0.1 equiv of ketone **5a** was monitored by HPLC (chiralcel OG column) after 2, 4.5, and 6 h, and it was found that the enantiomeric excess did not

full description cf. Wynberg, H.; Ten Hoeve, W. (Marion Laboratories INC) Eur. Pat. Appl. EP 0 342 903 A1 (Cl. C07D 303/48, C07B 57/00) 23/11/89. This paper, **7b**: HPLC, 33% ee, $[\alpha]_D = -48$ (c = 2.0, $CHCl_3$); lit. ~100% ee, $[\alpha]_D = -155.6$ (c = 2.0, $CHCl_3$).

(7) Mobile phase: *i*PrOH/hexane (10/90) for Chiralcel OG and *i*PrOH/hexane (25/75) for Chiralcel OD. Flow rate: 1 mL/min.

(8) Armstrong A.; Washington I.; Houk K. N. *J. Am. Chem. Soc.* **2000**, *122*, 6297−6298.

(9) During these first investigations it was found that the ketones **3a**, **3e**, **4a**, **4e**, and **5e** did not undergo Baeyer−Villiger oxidation within the reaction time. They were observed in the correct expected ratio in the ^{1}H NMR spectra of the crude products. However, ketone **5a** underwent Baeyer−Villiger oxidation at ambient under conditions **A** but was stable at 0 °C under conditions **B**. During experiment 8 (procedure **A**, Table 1) 77% (0.23 mmol) of a 25/75 mixture of **5a** and the BV-lactones were recovered in the crude product and 50% (0.15 mmol) of a 65/35 mixture of both oxidation products were isolated by chromatography (silica gel, AcOEt/hexane). The ^{1}H NMR are consistent with 3-fluoro-6-isopropyl-3-methyloxepan-2-one and 7-fluoro-4-isopropyl-7-methyloxepan-2-one. ^{1}H NMR (C_6D_6, 400 MHz): δ 0.53 (d, J = 7 Hz, 6H, isomer I), 0.55 (d, J = 7 Hz, 3H, isomer II), 0.59 (d, J = 7 Hz, 3H, isomer II), 1−1.7 (m, 6H isomers I and 6H isomer II), 1.29 (d, $^3J_{HF}$ = 19 Hz, 3H, isomer II), 1.52 (d, $^3J_{HF}$ = 23 Hz, 3H, isomer I), 2.42 (AA′ part of AA′XX′, 2H, isomer II), 3.73 (ddt, ^2J = 12 Hz, ^3J = 4 Hz, $^4J = {}^4J$ = 2 Hz, 1H, isomer I), 4.35 (dd, ^2J = 12 Hz, ^3J = 8.5 Hz, 1H, isomer I). ^{13}C NMR (C_6D_6, 100 MHz): isomer I *major*, δ 19.0, 19.3 (CH_3), 25.6 ($^3J_{CF}$ = 3.5 Hz, CH_2), 26.1 ($^2J_{CF}$ = 25 Hz, CH_3), 31.3 (CH), 35.4 ($^2J_{CF}$ = 26 Hz, CH_2), 44.8 (CH), 72.3 ($^3J_{CF}$ = 9 Hz, CH_2), 97.0 ($^1J_{CF}$ = 180 Hz, C), 170.5 ($^2J_{CF}$ = 24 Hz, C); isomer II *minor*, δ 18.5, 18.7 (CH_3), 25.8 ($^3J_{CF}$ = 3 Hz, CH_2), 28.2 ($^2J_{CF}$ = 27 Hz, CH_3), 33.5 (CH), 37.1 ($^2J_{CF}$ = 26 Hz, CH_2), 39.9 ($^3J_{CF}$ = 4 Hz, CH_2), 40.2 (CH), 113.6 ($^1J_{CF}$ = 229 Hz, C), 170.8 ($^2J_{CF}$ = 33 Hz, C). IR ($CHCl_3$): ν = 3620, 2960, 2880, 1730, 1440, 1390, 1320 cm^{-1}.

(10) Following procedure **B** at 0 °C and without ketone, no epoxidation was observed.

vary much with time during the reaction (39%, 38%, and 38%, respectively).

Using ketone **5a** (0.3 equiv), methyl ester **6a** was converted into (−)-epoxide **7a** having the (2*R*,3*S*)-configuration[11] with 40% ee using procedure **A** and 46% ee using procedure **B**. A slightly lower ee (33%) was however obtained upon epoxidation of the more hindered *tert*-butyl ester **6b** under the same conditions (procedure **A**, 0.3 equiv of ketone **5a**), Scheme 1.

Using ketone **5a** (0.1 equiv) and procedure **B** at 0 °C, *trans*-stilbene was converted into (−)-*trans*-stilbene oxide having the (*S*,*S*)-configuration[12] and 60% ee.

With all ketones except ketone **5e** (Table 1, line 7), the (−)-(2*R*,3*S*) epoxide **7a** was the *major* isomer. This could be rationalized by using the now classical spiro-approach shown in Figure 1, where the dioxirane corresponding to ketone **5a** was chosen as example.

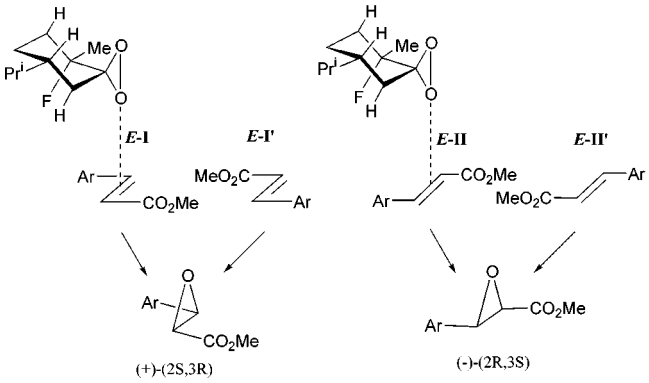


Figure 1.

The *axial* approaches, which are considered disfavored by steric interactions (as expected with cyclohexane-type substrates and as recently calculated on monofluorocyclohexanone[8]), should lead to a racemic (or close to racemic) mixture of the epoxide because of two identical *axial* protons (H3 and H5). The enantioselectivity should thus be due to the *equatorial* approaches, with ***E*-I** and ***E*-I′** disfavored because of F/Ar or F/Ester repulsive interactions compared to ***E*-II** and ***E*-II′** (which are probably similar) and one could predict that (2*R*,3S)-(−)-epoxide should be the *major* isomer as has been observed.

In the case of the hindered *tert*-butyl ester **6b**, the *equatorial* approaches also determine the enantioselectivity, but while, in the case of the methyl ester **6a**, both ***E*-II** and ***E*-II′** contribute to the formation of the (−)-epoxide, in the case of **6b**, ***E*-II′** becomes disfavored (the large *tert*-butyl group being pointed toward the ring) and only ***E*-II** (which probably remains energetically the same) provides the epoxide, thus resulting in a decrease in the (−)-enantioselectivity as observed.

Obtaining (−)-(*S*,*S*)-*trans*-stilbene epoxide is also fully consistent with this classical spiro-approach, Figure 1. In this case there are only four approaches, two *axial* disfavored and leading to a "racemic" mixture (***A*-I**, ***A*-II**) and two *equatorial* (***E*-I**, ***E*-II**), where ***E*-II** is preferred over ***E*-I**, thus providing the (−)-isomer.

In conclusion, it was found that α-fluoro ketone **5a** having an *axial*-fluorine was more efficient than α-fluoro ketone **5e** having an *equatorial*-fluorine, in consistency with *ab initio* predictions[8] which, although, concern only the last step. It was also shown that the effect of an *axial*-fluorine was stronger than the effect of an *axial*-chlorine. From methyl *p*-methoxycinnamate **6a**, (−)-epoxide **7a** was obtained with 82% conversion and 46% ee (procedure **B**, 0 °C and 0.3 equiv of ketone **5a**, Table 2) while *trans*-stilbene was epoxidized in 68% conversion and 60% ee. Considering the structure of ketone **5a**, four approaches (*axial*) among the eight possible ones (four *axial* and four *equatorial*) have equal probabilities and provide a "racemic" mixture. Therefore, the 46% and 60% ee values obtained are promising. Other halogenated ketones which are tetrasubstituted are already under study.

Acknowledgment. The authors thank Dr. A. Wick (SYLACHIM-Finorga-Paris) for financial support and encouragement and Dr. Dulery and Dr. Verne (Synthelabo Biomoleculaire-Strasbourg) for their help in ee determinations.

Supporting Information Available: NMR spectra of **5a**, **5e**, **7a**, **7b**, methanol-d_4 experiments, lactones derived from **5a**, and HPLC. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0001721

(11) For assignment of the (*2R*,*3S*)-configuration to (−)-**7a**, cf. Matsuki, K.; Sobukawa, M.; Kawai, A.; Inoue, H.; Takeda, M. *Chem. Pharm. Bull.* **1993**, *41*, 643−648. For assignment of (−)-**7b**, cf. ref 6.

(12) For assignment of the (*S*,*S*)-configuration to the (−)-stilbene oxide, cf. Imuta, M.; Ziffer, H. *J. Org. Chem.* **1979**, *44*, 2505−2509.