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Enzymatic Hydrolyses of the σ-Symmetric Dicarboxylic Diesters Bearing a Sulfinyl Group as the Prochiral Center

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Enzymatic hydrolyses of the σ-symmetric dicarboxylic diesters bearing a sulfinyl group as the prochiral center were examined by employing porcine liver esterase and procine pancreatic lipase. Eventually, their chiral half esters were elaborately obtained as the corresponding chiral phenacyl esters. The stereochemistry of the chiral half esters was determined by the X-ray analysis and their chemical correlations.

In the past decate from now, there have been a large number of papers on the enzymatic or non-enzymatic chiral induction onto prochiral σ-symmetric dicarboxylic derivatives.[1)] However, enzymatic hydrolysis of the σ-symmetric dicarboxylic diesters bearing a sulfinyl group as the prochiral center has never been attempted before our preliminary trial.[1, 2)] Herein we wish to report the first enzymatic hydrolyses of dicaboxylic diesters **1a-c** and reveal the stereochemistry of their resultant half esters **2a-c**.

Diesters **1a-c** were obtained in each high overall yield (72-86%) by esterification of commercially available 2, 2'-thiodiacetic acid with the corresponding alcohol in the presence of a catalytic amount of 98% H_2SO_4 under reflux followed by oxidation with *m*-chloroperbenzoic acid (1 mol eq) in CH_2Cl_2 at 0 °C. Thus, their enzymatic hydrolyses exploiting two kinds of enzymes were undertaken as follows. To a mixture of each diester **1a-c** (0.5 mmol) and 0.1 M phosphate buffer solution (pH 7.5, 10 ml) was added porcine liver esterase (PLE) (Sigma Type I, 100 units) with stirring. The whole mixture was stirred at 40 °C in an oil bath for 0.5 or 1 h and then adjusted to pH 1.9 with 1 N HCl. After evaporation of the reaction mixture *in vacuo*, the residue was dissolved in MeOH and then filtered through a celite bed. The filtrate was condensed *in vacuo* to give an oily residue which was purified on a resin column (SEPABEADS SP 207, Mitsubishi Chemical Ind. Ltd.) with water and then water-MeOH (7:3) as the eluent. Each resultant crude carboxylic acid **2a-c** was dissolved in water (10 ml). To the water solution was added Cs_2CO_3 (0.23 mmol) and the mixture was stirred at room temperature for 10 min. After evaporation *in vacuo*, the residue was treated with *N*, *N*-dimethylformamide (10 ml) and 2-bromoacetophenone (0.54 mmol) at room temperature for 30 min. The reaction mixture was

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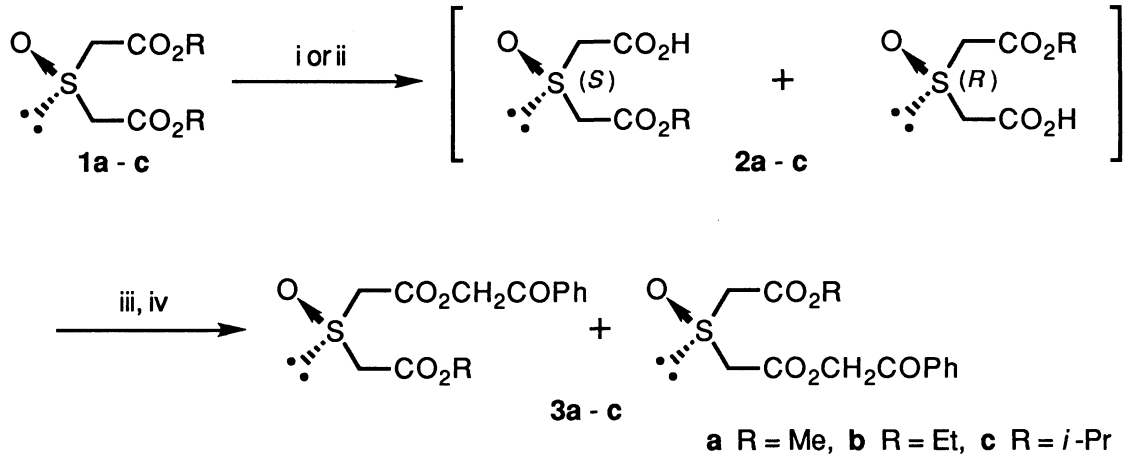


i) PLE (Sigma Type I, 200 units/mmol **1a-c**)/0.1 M phosphate buffer solution (pH 7.5)/40 °C; ii) PPL (Sigma Type II, 10^4 units/mmol **1a-c**)/0.1 M phosphate buffer solution (pH 8.0)/rt; iii) $CsCO_3$ (0.5 mol eq)/water/rt; iv) $PhCOCH_2Br$ (1.1 mol eq)/DMF/rt

Scheme 1.

Table 1. Enzymatic hydrolysis of σ-symmetric dicarboxylic diesters **1a-c**

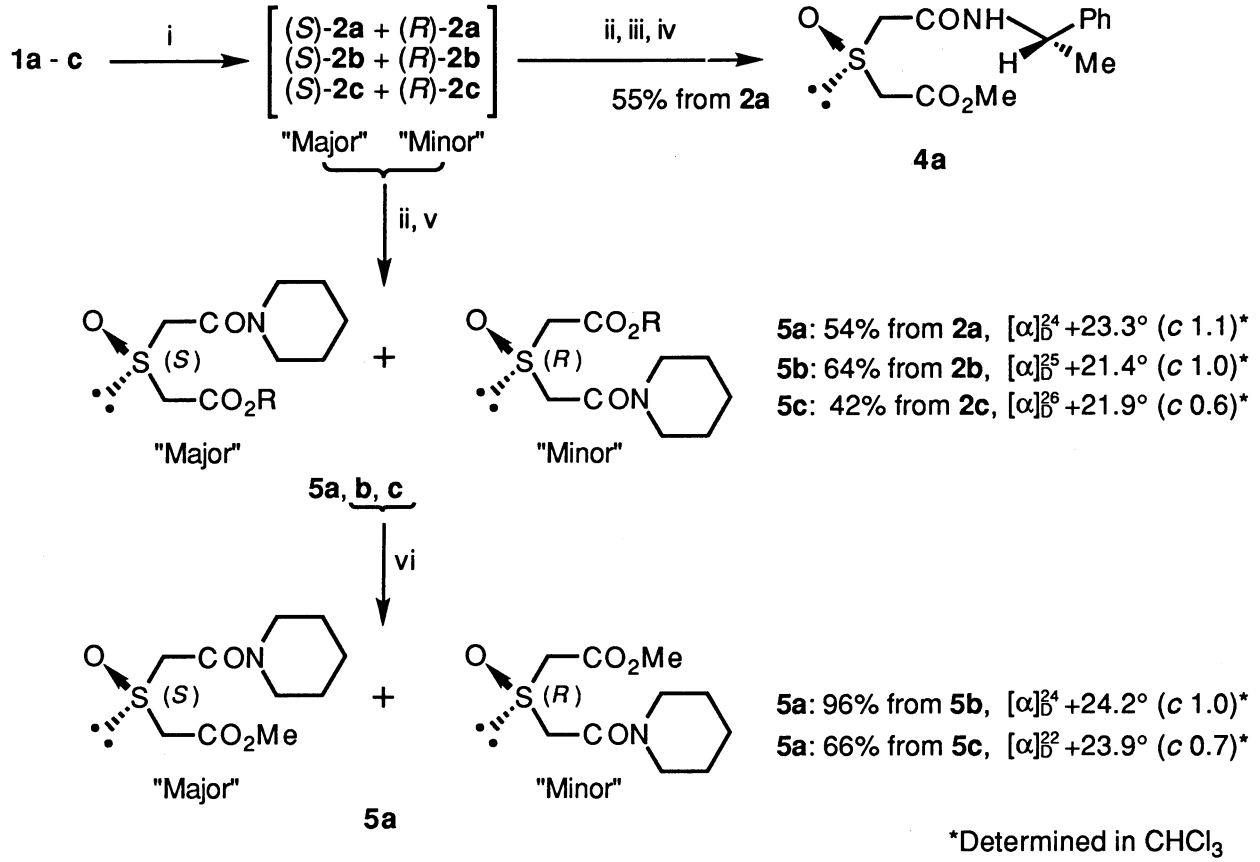
Entry	Substrate	Enzyme	Reaction time / h	Major product	Yield[a]/ % of **3a - c**	ee[b]/ % of **3a - c**
1	**1a**	PLE	0.5	(*S*)-**2a**	74	86
2	**1b**	PLE	0.5	(*S*)-**2b**	74	82
3	**1c**	PLE	1	(*S*)-**2c**	74	76
4	**1a**	PPL	12	(*R*)-**2a**	86	91[c]
5	**1b**	PPL	24	(*R*)-**2b**	92	83
6	**1c**	PPL	72	(*S*)-**2c**[d]	46	4

a) overall yield of **3a-c** from **1a-c**. b) Unless otherwise, determined by HPLC analysis [Chiralcell A(S)MBC 25 cm x 0.4 cm I.D. (Daicel)] using *n*-hexane-*i*-PrOH (1:1). c) Determined by ^{1}H-NMR (200 MHz, $CDCl_3$) analysis in the presence of 1 mol eq of Eu(hfc)3. d) 43% Recovery of **1c**.

submitted to the usual work-up to give each corresponding phenacyl ester **3a-c** as colorless needles from CH_2Cl_2 in 74% overall yield from **1a-c**, respectively (Entries 1-3 in Table 1). The enantiomeric excess (ee) values of **3a-c** were determined to be 86, 82, and 76%, respectively, by exploiting a high-performance liquid chromatography (HPLC) equiped with a chiral packed column [Chiralcell A(S)MBC, Daicel]. Similar enzymatic hydrolyses of **1a-c** employing porcine pancreatic lipase (PPL) have been done as follows. Namely, a mixture of each diester **1a-c** (0.50 mmol) and PPL (Sigma Type II, 5 x 10^3 units) in 0.1 M phosphate buffer solution (pH 8.0, 10 ml) was stirred at room temperature for each required time as shown in Table 1 (Entries 4-6). The same work-up of the reaction mixture as described above gave each corresponding phenacyl ester **3a**

(86% yield, 91% ee), **3b** (92% yield, 83% ee), or **3c** (46% yield, 4% ee), respectively. Interestingly, chiral recognition mode with PPL to the diesters **2a** and **2b** proved to be opposite to the case of PLE on the basis of the direction of their optical rotations [PLE: **3a** = $[\alpha]_D^{21}$ +45.2°, **3b** = $[\alpha]_D^{21}$ +40.1°; PPL: **3a** = $[\alpha]_D^{21}$ -50.9°, **3b** = $[\alpha]_D^{21}$ -37.6°. All data were determined in $CHCl_3$ (*c* 1.0).].[3)]

In order to determine the stereochemistry of the major half methyl ester **2a** produced by PLE-promoted hydrolysis of **1a**, **2a** was converted to its (*S*)-(-)-α-methylbenzylamine amide **4a** [colorless prisms, mp 111-



a R = Me, **b** R = Et, **c** R = *i*-Pr

i) PLE (Sigma Type I, 200 or 500 units/mmol **1a-c**)/0.1 M phosphate buffer solution (pH 7.5)/40 °C; ii) *N*-methylmorpholine (1.0 mol eq)/ClCO*t*-Bu (1.0 mol eq)/CH_2Cl_2/-15 °C; iii) (*S*)-(-)-α-methylbenzylamine (1.5 mol eq)/-15 °C; iv) Recrystallization from CH_2Cl_2-*n*-hexane; v) piperidine (1.5 mol eq)/-15 °C; vi) Et_3N (catalytic)/MeOH/reflux

Scheme 2.

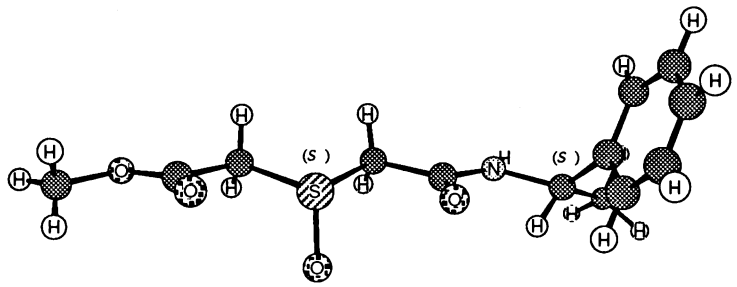


Fig. 3. Perspective view of the crystallographic structure of **4a**.

112.5°C, $[\alpha]_D^{25}$ -26.3° (*c* 1.0, $CHCl_3$)], which was submitted to the X-ray analysis.[4] As depicted in Fig. 1, the absolute configuration of the chiral sulfur atom was established to be *S* on the basis of the *S* configuration of the chiral methine carbon atom of the α-methylbenzylamine moiety. The absolute configuration of the chiral sulfur atom of each major component of compounds **2b** and **2c** obtained by PLE-promoted hydrolyses of **1b** and **1c**, was confirmed to be *S* by their chemical correlation with *S*-excess **2a** as shown in Scheme 2. Namely, methanolysis of the ester moiety of piperidine amides **5b** and **5c** derived from the corresponding compounds **2b** and **2c**, afforded methyl ester **5a** which was identical with the authentic compound obtained from the *S*-excess compound **2a**. Thus, the stereochemistry of the chiral sulfur atom of each major component of the half esters **2b** and **2c** generated by PPL-promoted hydrolyses of **1b** and **1c**, should be *R* configuration on the basis of the optical rotations of their phenacyl esters **3b** and **3c** as described above.

References

1) Y. Nagao and E. Fujita, *Yuki Gosei Kagaku Kyokai Shi*, **42**, 622 (1984); M. Ohno and M. Otsuka, *Org. React.*, **37**, 1 (1989) and references cited therein.

2) Y. Nagao, M. Kume, R. C. Wakabayashi, T. Nakamura, and M. Ochiai, The 13rd Symposium of Progress in Organic Reaction and Synthesis, Tokushima, Japan, 1986, symposium paper, pp 34-38; After introduction of our preliminary trial of the PLE- and PPL-promoted hydrolyses of **1a** in Ref. 1 (M. Ohno and M. Otsuka), enzymatic resolutions of racemic methyl sulfinylacetates were reported, see: K. Burgess and I. Henderson, *Tetrahedron Lett.*, **30**, 3633 (1989).

3) Y. Nagao, M. Kume, R. C. Wakabayashi, T. Nakamura, and M. Ochiai, *Chem. Lett.*, **1989**, 239; Y. Nagao, T. Tohjo, T. Kaneuchi, Y. Yukimoto, and M. Kume, *ibid.*, **1992**, 1817.

4) The crystallographic data of compound **4a** are follows. $C_{13}H_{17}NO_4S$, M= 283.34, orthorhombic, $P2_12_12_1$, a = 7.92(1) Å, b = 32.762(8) Å, c = 5.551(5) Å, V= 1439(2) $Å^3$, z = 4, Dcalc = 1.307 g/cm^3, R = 0.065.

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