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Efficient Preparation of New Chiral Synthons Useful for (+)-Carbacyclin Synthsis by Utilizing Enzymatic Hydrolysis of Prochiral σ-Symmetric Diesters[1)]

Yoshimitsu NAGAO,* Masaharu KUME, Robin Chikako WAKABAYASHI, Takeshi NAKAMURA, and Masahito OCHIAI
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611

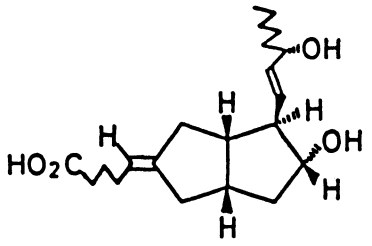
Enzymatic hydrolyses of some prochiral σ-symmetric dimethyl esters employing porcine liver esterase and porcine pancreatic lipase were investigated, resulting in the enantioselective preparation of the corresponding new monoesters useful for (+)-carbacyclin synthesis. It was also demonstrated that the hydrolysis with porcine liver esterase was remarkably affected by acetone as a co-solvent.

Enzymatic and nonenzymatic differentiations between two identical groups in prochiral molecules are currently interesting subjects in the field of asymmetric synthesis.[2)] Recently, we reported asymmetric synthesis of (+)-carbacyclin (1) and a useful synthetic intermediate for (+)-isocarbacyclin utilizing a nonenzymatic chiral induction method; diastereoselective thiolysis of 4(R)-methoxycarbonyl-1,3-thiazolidine-2-thione diamide (2) with benzene thiol in the presence of Et_3N.[3)] However, the asymmetric thiolysis of 2 was unsatisfied with respect to the diastereoselectivity (52% diastereomer excess).[3)] Therefore, we attempted enzymatic hydrolyses of cis-cyclohex-4-ene-1,2-bis(methyl acetate) (3), cis-cyclopentan-4-one-1,2-bis(methyl acetate) (4), and its ethylene acetal 5, whose chiral monoesters should be available as new chiral synthons for (+)-carbacyclin synthesis. To our knowledge, there has been no report on the enzymatic hydrolysis of meso carbocyclic bis(alkyl acetate) among the previous related papers.[4,5)] We now describe an efficient preparation of new chiral synthons 7, 8, and 10 by utilizing the enzyme-promoted hydrolyses of the corresponding diesters 3-5 and some useful new information about the reaction media for the enzymatic hydrolysis. Substrates, diesters 3-5 were readily synthesized from cis-cyclohex-4-ene-1,2-bis(acetic acid)[2a)] via a sequence of reactions shown in Scheme 1.

Enzymatic hydrolyses were carried out as follows. The diesters 3-5 (1 mmol) were added to a mixture of 0.1 M phosphate buffer solution (pH 7.5, 30 ml) and acetone (3 ml). After adding porcine liver esterase (PLE) (Sigma Type I, 800 units), the mixture was stirred at room temperature (ca. 24 °C) for the required time. The reaction mixture was adjusted at pH 3-4 with 10% HCl and then extracted with AcOEt. The usual work-up of the AcOEt extract gave the corresponding

monoesters (Entries 1,4, and 7 in Table 1). The PLE-catalyzed hydrolyses of the diesters 3-5 were tentatively performed in the reaction media without acetone (Entries 2,5, and 8 in Table 1).

The enzymatic hydrolyses of the diesters 3-5 (1 mmol) suspended in 0.1 M phosphate buffer (pH 8.0, 20 ml) in the presence of porcine pancreatic lipase (PPL) (Sigma Type II, 10^4 units) were similarly done. Through the entire reaction, 10% NaOH aqueous solution (1 mmol) was added in the following manner; 0.6 mmol after the reaction for 12 h and 0.4 mmol after the reaction for another 12 h. These results were summarized in Table 1 (Entries 3, 6, and 9).



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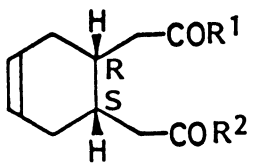
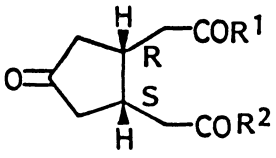
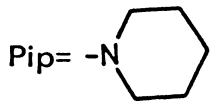


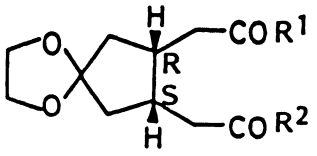
2 $R^1=R^2=T$
3 $R^1=R^2=OMe$
6 $R^1=OH, R^2=OMe$
7 $R^1=OMe, R^2=OH$
11 $R^1=Pip, R^2=OMe$
12 $R^1=OMe, R^2=Pip$
18 $R^1=SPh, R^2=OMe$



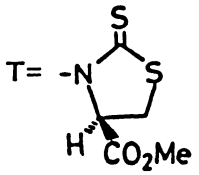
4 $R^1=R^2=OMe$
8 $R^1=OH, R^2=OMe$
9 $R^1=OMe, R^2=OH$
13 $R^1=SPh, R^2=OMe$
15 $R^1=OMe, R^2=SPh$



Pip= -N



5 $R^1=R^2=OMe$
10 $R^1=OH, R^2=OMe$
14 $R^1=SPh, R^2=OMe$



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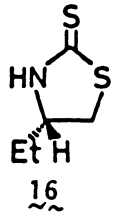

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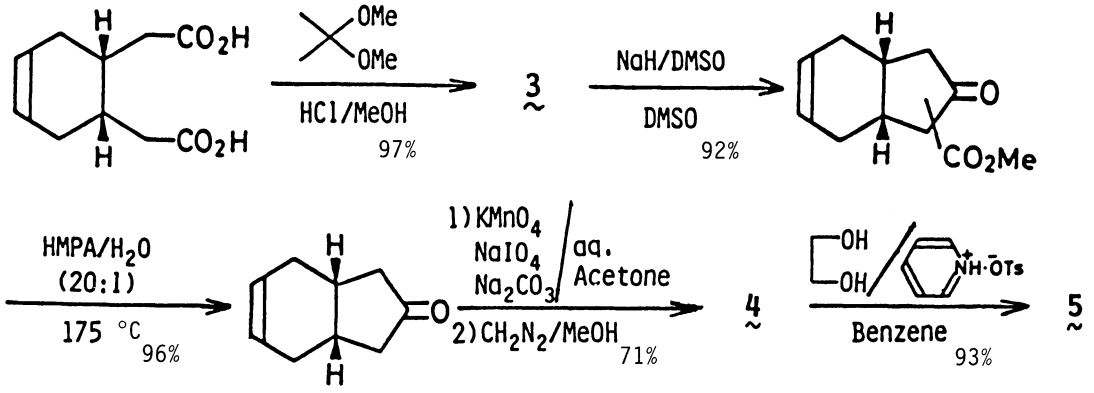
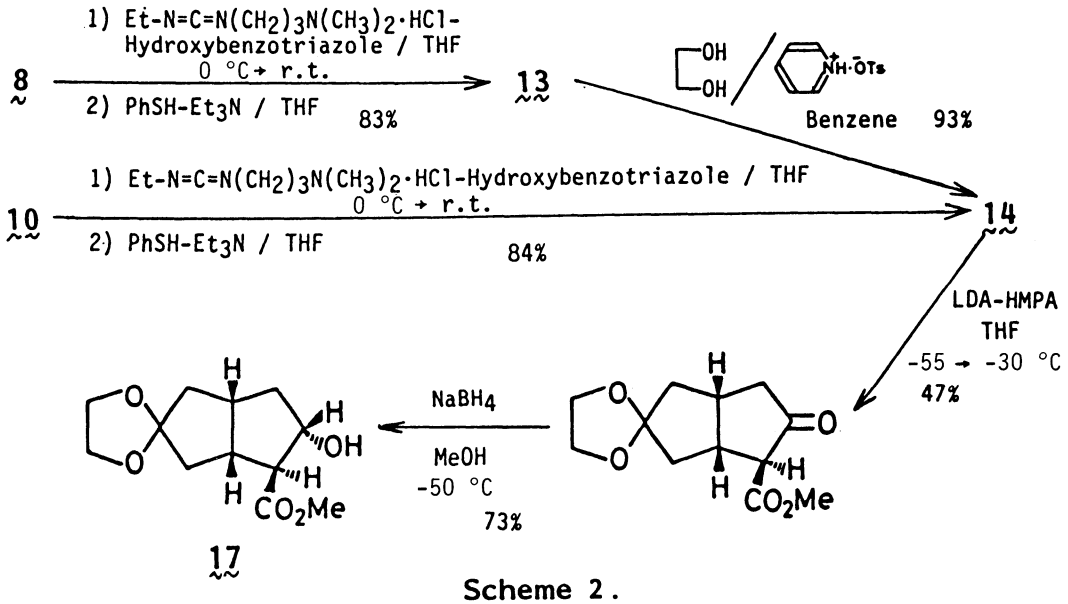


Scheme 1.

Table 1. Enzymatic hydrolyses of prochiral σ-symmetric dimethyl esters

Entry	Substrate	Enzyme	Reaction time/h	Product	Yield/% (isolated)	E.e./%
1	3	PLE	15	6 excess	98	22[d]
2[a]	3	PLE	1.3	6 excess[b]	91	76[d]
3	3	PPL	27	7 excess[b]	97	97[d]
4	4	PLE	50	8 excess[b]	86	88[e]
5[a]	4	PLE	2.5	8 excess	88	85[e]
6	4	PPL	180	9 excess	48	6[e]
7	5	PLE	25	10 excess[b]	99	90[d]
8[a]	5	PLE	1.8	10 excess	88	60[d]
9	5	PPL	122	none[c]	—	—

a) Without acetone. b) Optical rotation of these compounds was determined in $CHCl_3$. 76% ee of 6 : $[\alpha]_D^{21}$ -2.5°(c 3.8), 97% ee of 7 : $[\alpha]_D^{22}$ +3.1°(c 11.8), 88% ee of 8 : $[\alpha]_D^{21}$ +1.9°(c 12.2), 90% ee of 10 : $[\alpha]_D^{22}$ -0.1°(c 13.2). c) Recovery (85%) of 5. d) Determined by HPLC analysis of 4(S)-ETT 16 amide of the corresponding monocarboxylic acid. e) Determined by specific rotation of the derivatives 14 and 15.



Scheme 2.

The absolute configurations of monoesters 6 and 7 were confirmed by their chemical conversion to the known compounds 11[2a] and 12,[2a] respectively. The stereochemical structures of monoesters 8-10 were determined by chemical conversion of compounds 8 and 10 to the known compound 17 [$[\alpha]_D^{24}$ -25.0° (c 1.0,

$CHCl_3$); lit.[5] $[\alpha]_D^{23}$ -28.8° (c 1.0, $CHCl_3$)] via compound 14 (Scheme 2) and by comparison of the specific rotation of the half-thiol diester 13 with that of 15 - small excess compound derived from 9. Compound 7 [97% enantiomeric excess (e.e.)] was readily converted to a synthetic intermediate 18[3a] [78% yield, $[\alpha]_D^{22}$ -3.8° (c 2.8, $CHCl_3$)] of (+)-carbacyclin (1) in the similar manner to the case of the reaction 8 ⟶ 13 shown in Scheme 2. Chiral monoesters 8 (88% e.e.) and 10 (90% e.e.) would be useful not only for the (+)-carbacyclin synthesis but also for syntheses of some natural products such as brefeldin,[6a] coriolin,[6b] and hirstic acid.[6c]

From these enzymatic hydrolyses, we recognized the following facts. 1) PLE can preferentially hydrolyze the (R)-site ester moiety but PPL can inversely hydrolyze the (S)-site ester moiety except for the case of acetal 5. 2) Acetone evidently affects the PLE-catalyzed chiral recognition of the diesters (See entries 1, 2, 7, and 8 in Table 1). 3) PLE-catalyzed hydrolyses without acetone as a co-solvent are generally very rapid.

References

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