Tetrahedron Letters,Vol.29,No.32,pp 3951-3954,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

Enantioselective Hydrolysis of Dialkyl 3-Monosubstituted Glutarates with Pig Liver Esterase: Structure-Optical Purity Relationships[1]

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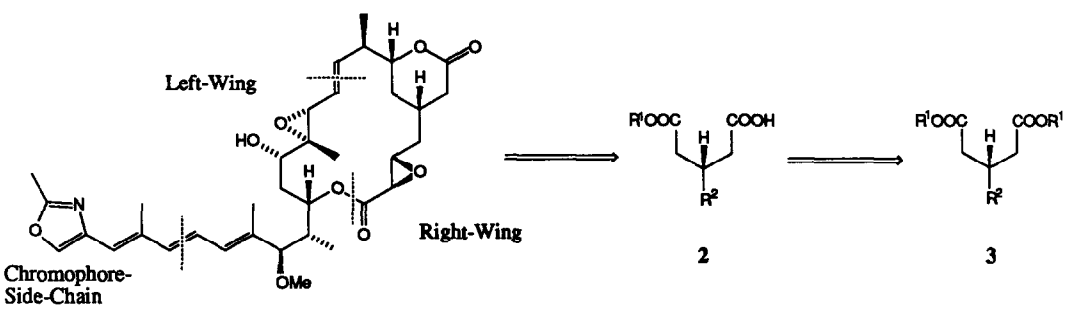
Summary: *Dialkyl 3-monosubstituted glutarates are subjected to hydrolysis with pig liver esterase to afford the corresponding chiral half-esters. Synthetically useful half-esters of higher optical purity are obtained from the prochiral substrates of more hydrophobic nature.*

Continuing efforts in our laboratories have focussed on the design and construction of novel chiral synthons prepared with enzymes starting from prochiral or meso diesters and on the application to natural product synthesis based on symmetrization-asymmetrization concept[2].

Scheme 1 *Synthetic Strategy for the Right-wing of Rhizoxin*



The retrosynthetic analysis of the right wing of rhizoxin[3,4] based on the synthetic strategy (Scheme 1) generated optically active half-esters **2** as the most suitable chiral synthons. Such optically active esters **2** are expected to be formed from the symmetrical glutarates **3** by asymmetric hydrolysis with pig liver esterase (PLE) and seem to be also valuable synthons in the synthesis of other natural products, because such basic structures having the functionalized substituents at C-3 position of glutarate are not readily available from chiral pool of natural origin and could be converted into various useful intermediates. However, simple dimethyl 3-monoalkyl glutarates afford the corresponding half esters with PLE generally in low optical yields[5] (17-54 % ee) except 3-methyl substrate (79-90 % ee).

We wish to report here that the optical yields of the half-esters **2** obtained by treatment of 3-monosubstituted glutarates with PLE can be improved considerably in response to structural changes of the prochiral substrates **3**. The efficient preparation of the prochiral diesters **3** was first investigated, because the easy availability of the prochiral substrates is very important as well as the optical purity of the chiral half-esters **2** in the symmetrization-asymmetrization strategy[2]. Three approaches were carefully studied. They are (A) cuprate addition (3-butenylmagnesium bromide-CuI) to dimethyl-2-penten-1,5-dioate, (B) Wittig reaction of dimethyl-3-oxoglutarate and various ylides, and (C) Michael addition of dimethyl malonate to various α,β-unsaturated esters. The most satisfactory results were obtained from the third approach as shown in Scheme 2. Any α,β-unsaturated esters can be prepared from the aldehydes (R^2-CHO) and phosphonates $(EtO)_2P(O)CH_2CO_2R^1$ (entry, 1,5,6,7,8,9 and 10). The second approach afforded the symmetrical diesters of entry 2,3 and 4 by the following multistep reactions. The Wittig products were obtained in 90 % yield from the reaction of dimethyl 3-oxoglutarate and $Ph_3P{=}CHCO_2Bzl$ in the presence of $PhCO_2H$ in C_6H_6 (reflux,24h). After hydrogenation (H_2/Pd-C), and conversion to acid chloride ($(COCl)_2$) followed by Rosenmund reduction (H_2/Pd-$BaSO_4$), the resulted aldehyde was further treated with $Ph_3P{=}CHCHO$, and the product was reduced with $NaBH_4$ to afford the allylic alcohol (entry 2) in 60 % yield. The Wittig reaction proceeded only in the case of stabilized ylids and gave satisfactory results in the presence of a catalytic amount of $PhCO_2H$. The starting material was simply recovered from the first approach. Therefore, Scheme 2 represents a general and efficient method for 3-monosubstituted glutarates[7].

Thus, each 3-monosubstituted glutarate (1 mmole scale) was subjected to asymmetric hydrolysis and the results were shown in Table 1[8]. Chemical yields were almost quantitative in all cases, but the optical purity is delicately controlled by the structural changes of the prochiral diesters. A simple oxygen-containing substituent (entry 1) afforded the half-ester in poor optical purity as observed in usual cases[5] and a hydroxysubstituent (entry 2) was found to be very poor substrate from a point of view of optical purity. However, protection with DHP or DHP-4-OMe (entry 3 or 4) increased the optical purity considerably. This observation brought us to look into more hydrophobic substrates or substrates having unsaturated substituents. The benzyl group (entry 5) was found to be almost equal to THP derivative (entry 3), but styryl (entry 6) and cinnamyl (entry 8) groups remarkably increased the optical yields of the half-esters. The presence of the double bond at proper position from the prochiral center seems to be very important in the optical purity. Although the phenethyl group (entry 7) gave poor result (44 % ee), 3-phenylpropyl group (entry 10) again gave a better optical yield. The exchange of the ester group from methyl to ethyl (entry 9) somewhat but clearly increased the optical purity (88 % ee to 91 % ee). For the synthetic purpose to **1**, the cinnamyl group was most ideal, because it is efficiently synthesized and the high optical purity of the half-ester could be applied to the natural product synthesis after cleavage of the double bond. Furthermore, a crystalline δ-lactone **4**, mp 89 °C, derived from the half-ester was obtained easily in optically pure state by single recrystallization. The absolute configuration of **2** (R^1=Et, R^2=CH_2-CH=CHPh) was correlated by comparison with previously assigned δ-lactone **6** or by conversion to 3-ethylvalerolactone **6** as shown in Scheme 3. The lactone **6** showed $[\alpha]_D^{20}$ +24.8° (*c* 1.28, $CHCl_3$), but known (3S)-ethylvalerolactone shows $[\alpha]_D^{20}$ -20.4° (*c* 1, $CHCl_3$)[9]. Therefore, the absolute configurations of **6** and **2** (R^1=Et, R^2=CH_2-CH=CHPh) were assigned to R- and S-configurations, respectively. Scheme 3 also illustrates the synthetic utility of the half-esters for the potential chiral synthons in natural product synthesis[10].

Scheme 2 *General Synthesis of 3-Monosubstituted Glutarates*

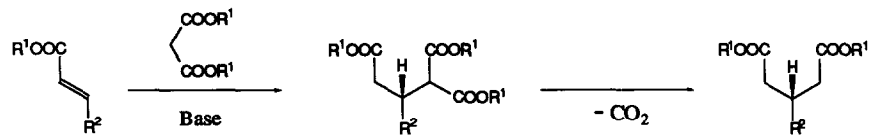
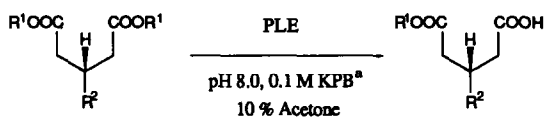


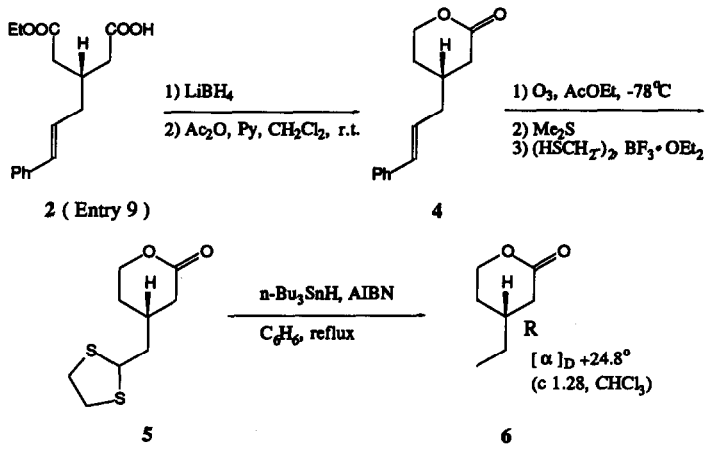
Table 1 *Enantioselective Hydrolysis of 3-Monosubstituted Glutarates with PLE*



Entry	R^1	R^2	C.Y.(%)	Opt.Purity(%e.e.)[c]
1	Me	$(CH_2)_2OBzl$	100	54
2	Me	$CH_2CH{=}CHCH_2OH$[b]	100	19
3	Me	$CH_2CH{=}CHCH_2OTHP$[b]	95	74
4	Me	$CH_2CH{=}CHCH_2OTHP\text{-}4\text{-}OMe$[b]	92	53
5	Me	CH_2Ph	98	73
6	Me	$CH{=}CHPh$[b]	100	93
7	Me	CH_2CH_2Ph	98	44
8	Me	$CH_2CH{=}CHPh$[b]	95	88
9	Et	$CH_2CH{=}CHPh$[b]	100	91
10	Me	$(CH_2)_3Ph$	97	88

a Each reaction was run in 25 ml of potassium phosphate buffer solution.
b The stereochemistry of the double bond is trans-configuration.
c Each half-ester was converted to the corresponding t-butyl ester (isobutene-catalytic conc.H_2SO_4) and the optical purity was determined by 1H-NMR by using $Eu(hfc)_3$.

Scheme 3 *Conversion to Various δ-Lactones*



2 (Entry 9) 4 5 6

Acknowledgment: This work was financially supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (No.62616005) from the Ministry of Education, Science, and Culture of Japan.

References and Notes:

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2. M. Ohno, "Enzymes in Organic Synthesis" Ciba Foundation Symposium, **111**, 171 (1985).
3. S. Iwasaki, M. Namikoshi, H. Kobayashi, J. Furukawa, S. Okuda, A. Itai, A. Kasuya, Y. Iitaka, and Z. Sato, *J. Antibiotics*, **39**, 424 (1986).
4. Rhizoxin is a biologically interesting new antitumor macrolide recently isolated and has the unique structural features[3]. It was divided into three moieties, right-wing, left-wing, and chromophore side-chain from a synthetic point of view. The synthetic study on the left-wing including the chromophore side-chain of **1** is now in progress and the results will be described soon in separate papers.
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6. C.Rüchardt, S.Eichler, and P.Panse, *Angew. Chem., Int. Ed.*, **2**, 619 (1963).
7. Detailed characterization of each compound will be published soon, and all materials described here gave satisfactory MS, IR and ^{1}H NMR spectra consistent with their structures.
8. All of the 3-monosubstituted glutarates were separately subjected to hydrolysis without pig liver esterase under the same conditions and confirmed to be almost stable at pH 8.0.
9. J. B. Jones, K.P.Lok, *Can. J. Chem.*, **57**, 1025 (1979).
10. Part of the results described here were presented at the 104th (1984) and 105th (1985) annual meetings of the Pharmaceutical Society of Japan (abstracts p. 625 and 141, respectively).

(Received in Japan 14 March 1988)