Pure & Appl. Chem., Vol. 64, No. 8, pp. 1121–1124, 1992.
Printed In Great Britain.

Synthetic study on an antitumor antibiotic rhizoxin by using an enzymatic process on prochiral β-substituted glutarates

Susumu Kobayashi,* Masahisa Nakada, and Masaji Ohno

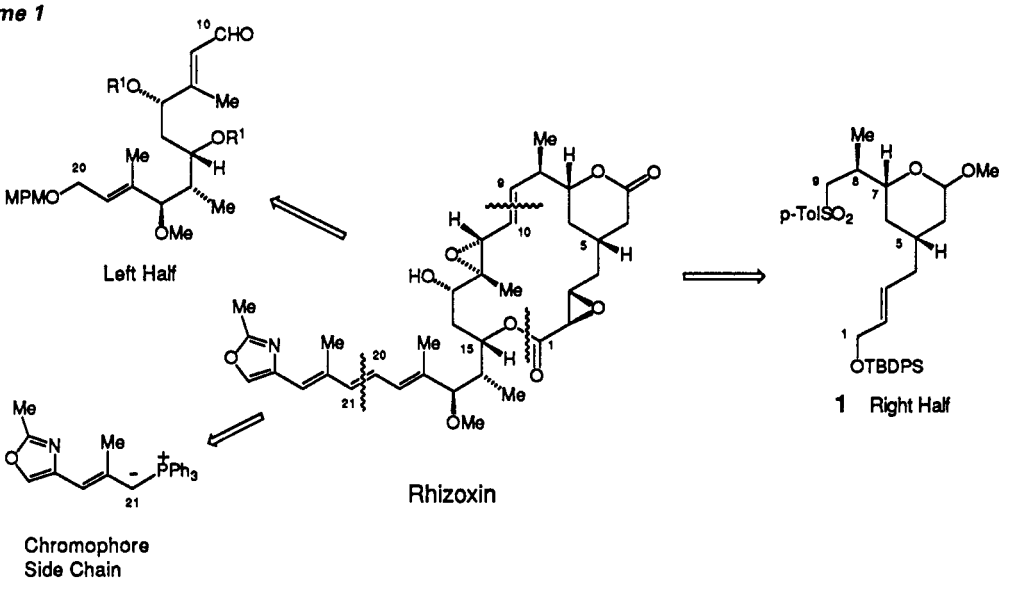
Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Abstract

Enantio- and stereoselective synthesis of the right-half segment (**1**, C_1-C_9) of macrolide antibiotic rhizoxin was achieved by enzymatic approach. Characteristic features of the present synthesis are (1) enantioselective hydrolysis of prochiral β-substituted glutarates with pig liver esterase, and (2) stereoselective cyclichydroboration of the 1,5-diene **8**.

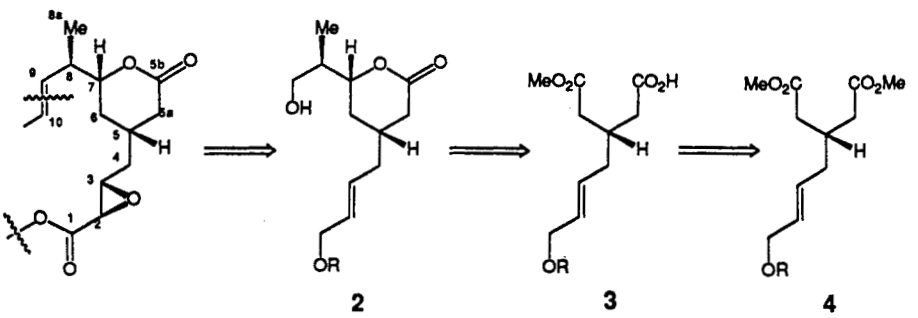
Rhizoxin is an antitumor antibiotic isolated as a toxin from the culture broth of *Rhizopus chinensis* which is a potent pathogen of rice seedling blight.[1] We have been investigating the total synthesis of this novel macrolide antibiotic based on the retrosynthetic analysis shown in Scheme 1. This paper describes the synthesis of the right-half segment (**1**, C_1-C_9) of rhizoxin by enzymatic approach using PLE.

Scheme 1



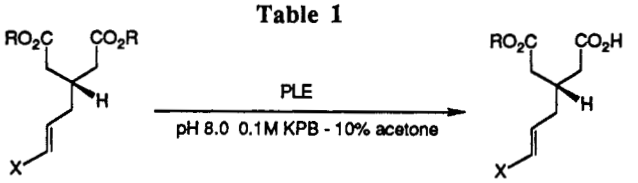
The absolute and even the relative stereochemistry have not been fully established when we started the synthetic study. Therefore, the synthetic strategy was desired to be flexible in order to be able to prepare all stereoisomer from the common intermediate in a stereocontrolled manner. Since we recognized a hidden symmetry in the right-half segment of rhizoxin (Scheme 1), we were interested in the enzymatic hydrolysis of β-substituted glutarates.[2] (Scheme 2) Usefulness of the enzymatic approach has already been demonstrated in the synthesis of biologically interesting compounds such as carbapenem, nucleoside, and aminocyclitol antibiotics.[3]

Scheme 2



Various β-substituted glutarates were prepared and were subjected to an enzymatic hydrolysis with PLE. Some typical results are shown in Table 1.[4] Chemical yields were almost quantitative in all cases, but the enantiomeric excesses varied delicately according to the size and the functional group. When hydroxyl derivative was employed as a substrate, the enantiomeric excess was found very poor (19%, entry 1). However, the enantiomeric excess was improved to 74% e.e. by protecting the hydroxyl group with tetrahydropyranyl group. (entry 2) These results clearly demonstrates the hydrophobic nature of the

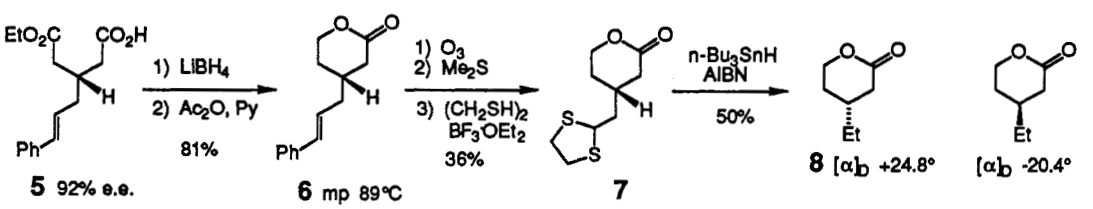
Table 1



entry	R	X	yield (%)	e.e. (%)
1	Me	CH_2OH	99	19
2	Me	CH_2OTHP	95	74
3	Me	Ph	97	88
4	Et	Ph	99	92

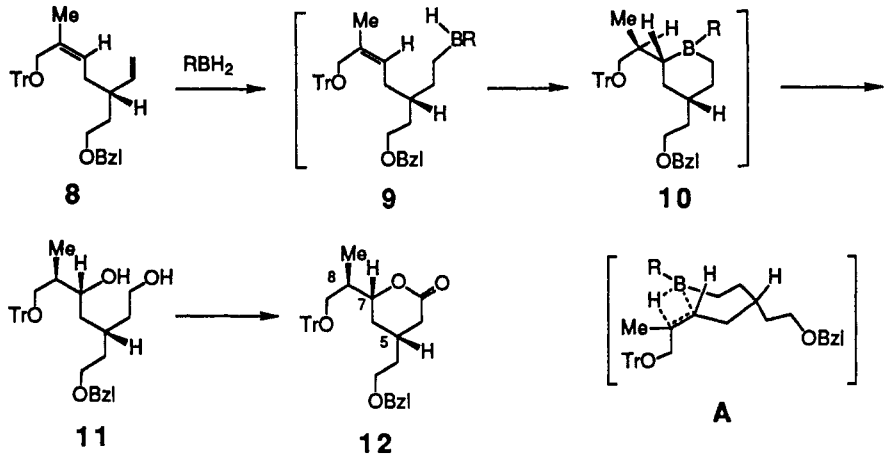
binding site of PLE. Further, the higher enantiomeric excess was achieved with the cinnamyl derivatives (entry 3,4). Enantiomeric excesses were determined by ^{1}H-NMR experiment using chiral shift reagent after transforming the carboxyl group to the *t*-butoxycarbonyl group. Scheme 3 shows the determination of the absolute configuration of the cinnamyl derivative **5** (entry 4). Comparison of the $[\alpha]_D$ value of the derived δ-lactone **8** with that in the literature[5] established the absolute configuration of the monoester **5**. Since enantiomerically pure δ-lactone **6** was easily obtained by simple recrystallization, we decided to use **6** as a starting material.

Scheme 3



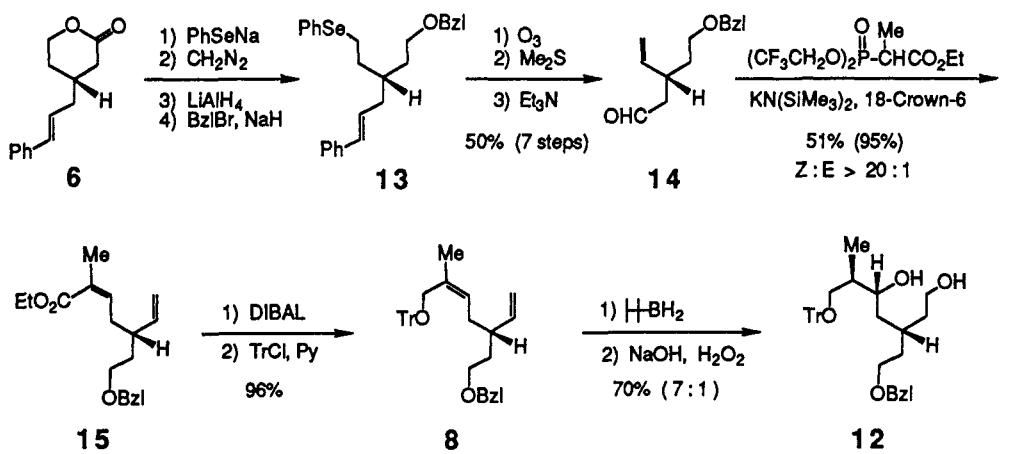
We examined two approaches, which are aldol-type reaction and hydroboration strategies. Aldol-type strategy seemed straightforward, but the degree of 1,3-asymmetric induction was found rather low when an achiral nucleophile such as vinyloxyborane or crotyl tin reagent was employed. Our synthetic effort was then focused on the alternative hydroboration approach.[6] (Scheme 4) We envisaged that on

Scheme 4



treatment of **8** with a monoalkylborane hydroboration would occur at the terminal olefin first, and that the resulting dialkylborane **9** was expected to undergo stereoselective intramolecular hydroboration. Since hydroboration proceeds with cis addition, the boat transition state **A** which will afford the desired **12** seemed most favorable. It should be emphasized here that all chiral centers in **12** can be controlled by this hydroboration strategy. The relative stereochemistry at C_7[7] and C_8 is determined by the geometry of the trisubstituted olefin, and the chiral center at C_7 is induced from the chiral center at C_5 by the intramolecular hydroboration of **9**. Since both enantiomer of **8** can be prepared from the chiral monoester **5**, two chiral centers at C_7 and C_8 can be controlled. The stereocontrol at C_5 is also possible by oxidizing either the hydroxyethyl group or the benzyloxyethyl group in **11**. These two groups are functionally equivalent.

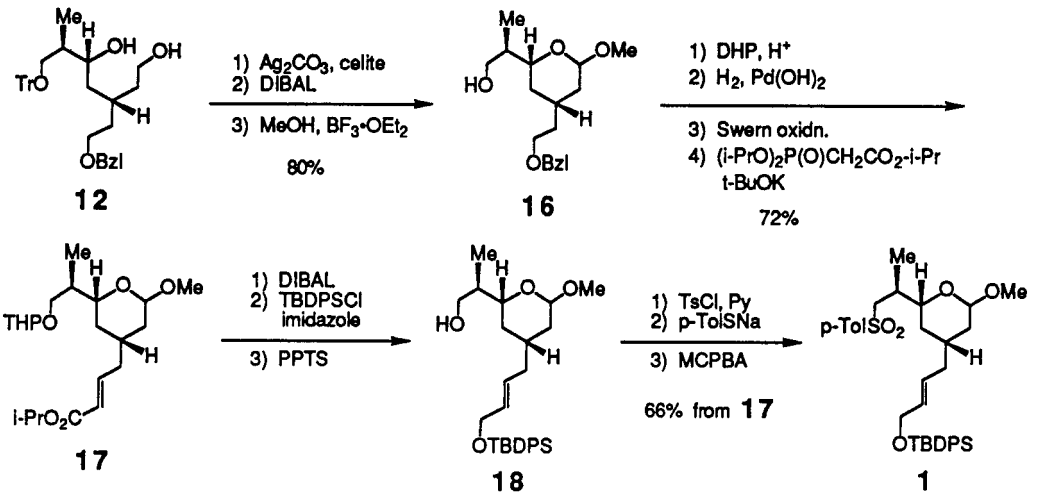
Scheme 5



The diene **8** was prepared by the sequence shown in Scheme 5. The requisite Z-olefin was selectively constructed by Wittig-Horner reaction using bis(trifluoroethyl)phosphonate reagent.[8] As expected the diene **8** underwent stereoselective cyclic hydroboration with thexylborane affording the desired diol **12** in 70% yield as a major isomer.[9] Two chiral centers, C_7 and C_8, were thus established.

Scheme 6 shows the final transformation of **12** to the right half segment **1**. Diol **12** was oxidized to δ-lactone, and the latter was reduced and protected as a hemiacetal. Two carbon unit (C_1-C_2) was introduced by Wittig-Horner reaction, and finally the alcohol **18** was converted to the sulfone **1**.

Scheme 6



In conclusion, the enantio- and stereoselective synthesis of the right half segment (**1**) of rhizoxin was achieved by the reasonable combination of enzymatic and chemical procedures. Particularly, PLE-mediated enantioselective hydrolysis of prochiral β-substituted glutarates would provide a potential chiral synthons, and the enzymatic approach is considered to be a useful and powerful methodology for enantioselective synthesis of biologically interesting compounds.

Acknowledgement

We thank Professor S. Iwasaki (University of Tokyo) for helpful discussion.

REFERENCES AND NOTES

1. S. Iwasaki, M. Namikoshi, H. Kobayashi, J. Furukawa, S. Okuda, A. Itai, A. Kasuya, Y. Iitaka, and Z. Sato, *J. Antibiot.*, **39**, 424 (1986).
2. (a) F. Huang, L. F. H. Lee, R. S. D. Mittal, P. R. Ravikumar, J. A. Chan, C. J. Sih, E. Caspi, and C. R. Eck, *J. Am. Chem. Soc.*, **97**, 4144 (1975). (b) M. Ohno, S. Kobayashi, T. Iimori, Y.-F. Wang, and T. Izawa, *ibid.*, **103**, 2405 (1981). (c)P. Mohr, N. Waespe-Sarcevic, C. Tamm, K. Gawronska, and J. K. Gawronski, *Helv. Chim. Acta*, **66**, 2501 (1983).
3. K. Adachi, S. Kobayashi, and M. Ohno, *Chimia*, **40**, 311 (1986).
4. M. Nakada, S. Kobayashi, M. Ohno, S. Iwasaki, and S. Okuda, *Tetrahedron Lett.*, **29**, 3951 (1988).
5. J. B. Jones and K. P. Lok, *Can. J. Chem.*, **57**, 1025 (1979).
6. W. C. Still and K. P. Darst, *J. Am. Chem. Soc.*, **102**, 7385 (1980).
7. The carbon numbers are expressed according to the rhizoxin numbering in this paper.
8. W. C. Still and C. Gennari, *Tetrahedron Lett.*, **24**, 323 (1983).
9. Almost no stereoselection was observed when diborane was used instead of thexylborane.
10. This paper is dedicated to the late Professor Shigenobu Okuda, University of Tokyo.