Tetrahedron Letters No. 31, pp 2741 - 2744.

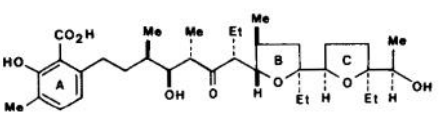
0040-4039/78/0729-2741$02.00/0

SYNTHETIC STUDIES ON POLYETHER ANTIBIOTICS. II.[1] STEREOCONTROLLED SYNTHESES OF EPOXIDES OF BISHOMOALLYLIC ALCOHOLS.

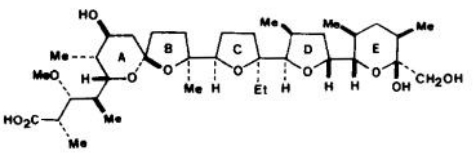
T. Fukuyama, B. Vranesic, D. P. Negri, and Y. Kishi*
Department of Chemistry, Harvard University
12 Oxford Street, Cambridge, Massachusetts 02138, U.S.A.

(Received in USA 18 April 1978; received in UK for publication 1 June 1978)

In connection with investigations directed toward the total synthesis of polyether antibiotics such as lasalocids and monensins,[2] we have studied synthetic methods to construct tetrahydrofurans 6 and 7 from acyclic precursors. Tetrahydrofurans 7 represent ring C of isolasalocid A[3] (1) and also ring C of monensin[3] (2), while tetrahydrofurans 6 represent ring B of isolasalocid A (1) and hopefully ring D of monensin (2).



1 : isolasalocid A

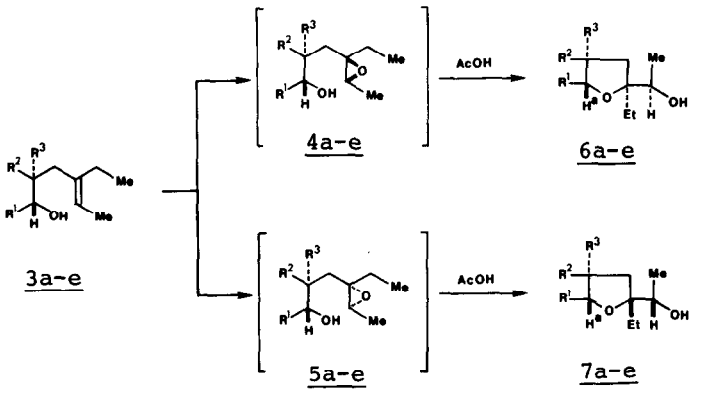


2 : monensin

Synthesis of Tetrahydrofurans 6

We first examined the degree of stereospecificity on epoxidizing bishomoallylic alcohols[4] 3a-e under various conditions. The resultant epoxide mixture was directly converted to tetrahydrofurans 6a-e and 7a-e by treatment with acetic acid at room temperature, and then the ratio of 6 and 7 was determined[5] (see Scheme 1). The stereochemistry of tetrahydrofurans 6 and 7 was assigned based on the observation that the chemical shift of the H^a proton in 6 was more effected by $Eu(fod)_3$ than that in 7. The assignment was later confirmed by the fact that lasalocid A was successfully synthesized from a compound similar to 6.[1] The results are summarized in Table 1. It is now clear that the Sharpless procedure[6] provides the tetrahydrofurans 6a-e in high stereospecificity. Examination of Dreiding models reveals that the transition state[7] of the minor epoxide (B) will experience more steric compression due to the interaction between the R^3 and ethyl groups than will the major epoxide (A).[8] This steric compression will become more serious in the case of $R^3=CH_3$ than for $R^3=H$ (compare the ratio in the c series with that in b and also in a).

Scheme 1



a : R^1=Pr^i, R^2=R^3=H

b : R^1=Pr^i, R^2=CH_3, R^3=H

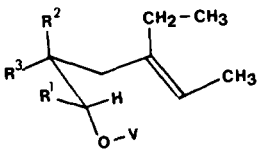
c : R^1=Pr^i, R^2=H, R^3=CH_3

d : R^1=*p*-$CH_3OC_6H_4$, R^2=R^3=H

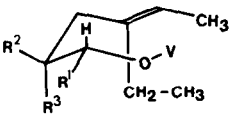
e : R^1=*p*-$CH_3OC_6H_4$, R^2=CH_3, R^3=H

Table 1

3	1) epoxidation (conditions shown below) 2) AcOH/RT → 6 + 7[5]	
a	MCPBA/CH_2Cl_2/RT	1 : 1
	$Mo(CO)_6$/*t*-BuOOH/C_6H_6/reflux	7 : 1
	$VO(acac)_2$/*t*-BuOOH/C_6H_6/reflux	7 : 1
	$VO(acac)_2$/*t*-BuOOH/C_6H_6/RT	9 : 1
b	$VO(acac)_2$/*t*-BuOOH/C_6H_6/RT	6 : 1
c	$VO(acac)_2$/*t*-BuOOH/C_6H_6/RT	>20 : 1
d	$VO(acac)_2$/*t*-BuOOH/C_6H_6/RT	8 : 1
e	$VO(acac)_2$/*t*-BuOOH/C_6H_6/RT	8 : 1



A

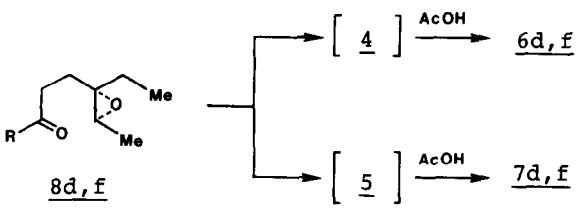


B

Synthesis of Tetrahydrofurans 7

All attempts to stereospecifically synthesize the epoxides 5 from the bishomoallylic alcohols 3 or their derivatives such as acetate, benzoate, trimethylacetate, trimethylsilyl ether, etc., were unsuccessful. Therefore, reduction of epoxy-ketones 8, readily prepared from the corresponding keto-olefins, to the epoxides 5 was investigated. Stereospecificity was again determined after acetic acid workup[5] (see Scheme 2). The results are summarized in Table 2. Thus,

Scheme 2



8d,f

d : R=*p*-$CH_3OC_6H_4$

f : R=CH=CH_2

the desired epoxides 5 can be synthesized with a high degree of stereospecificity by using a combination of lithium aluminum hydride and *dl*-2-(*o*-2-toluidinomethyl)pyrrolidine.[1] It is interesting to point out that all lithium aluminum hydrides tested gave the stereospecificity to some extent, but borohydrides including L-Selectride did not. This may indicate that coordination of aluminum to the epoxide and ketone oxygens plays an important role in bringing about a stereospecific reduction. The scope and limitation of this new procedure for various keto-epoxides is currently under investigation. Successful application of this procedure for the total synthesis of lasalocid A will be reported in the following communication. Use of this method for the total synthesis of monensin is in progress.

Table 2

	1) reduction (conditions shown below) 2) AcOH/RT	6 + 7[5]
8	→	
d	$NaBH_4$/methanol/RT	1 : 1
	L-Selectride/ether/RT	1 : 1
	$LiAlH_4$/ether/0°C	1 : 3
	$LiAlH(OBu^t)_3$/ether/0°C	1 : 4
	$LiAlH_4$/diamine[1]/ether/-78°C	1 : 11
f	$LiAlH_4$/diamine[1]/ether/-78°C	1 : 10

Acknowledgment Financial support from National Institutes of Health, National Science Foundation, and Hoffmann-La Roche Company is gratefully acknowledged.

References and Footnotes

1. For Part I of this series, see T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, J. Am. Chem. Soc., in press.
2. Reviews: J. W. Westley, Adv. Appl. Microbiol., 22, 177 (1977), and Ann. Rep. Med. Chem., 10, 246 (1975); B. C. Pressman, Ann. Rev. Biochem., 45, 501 (1976)
3. See the references cited in the reviews under reference 2.
4. Satisfactory spectroscopic data were obtained for all new compounds.
5. The ratio of 6 and 7 was determined by VPC and/or by preparative layer chromatographic separation.
6. K. B. Sharpless and R. C. Michaelson, J. Am. Chem. Soc., 95, 6136 (1973); S. Tanaka, H. Yamamoto, H. Nozaki, K. B. Sharpless, R. C. Michaelson, and J. D. Cutting, J. Am. Chem. Soc., 96, 5254 (1974).
7. For the mechanism of the vanadium catalyzed epoxidation of olefins, see A. D. Chong and K. B. Sharpless, J. Org. Chem., 42, 1587 (1977).
8. The zigzag conformation of 3 was assumed as the preferred conformation.